Morphologic Mimics in Dermatopathology: Diagnostic Blunders to Avoid

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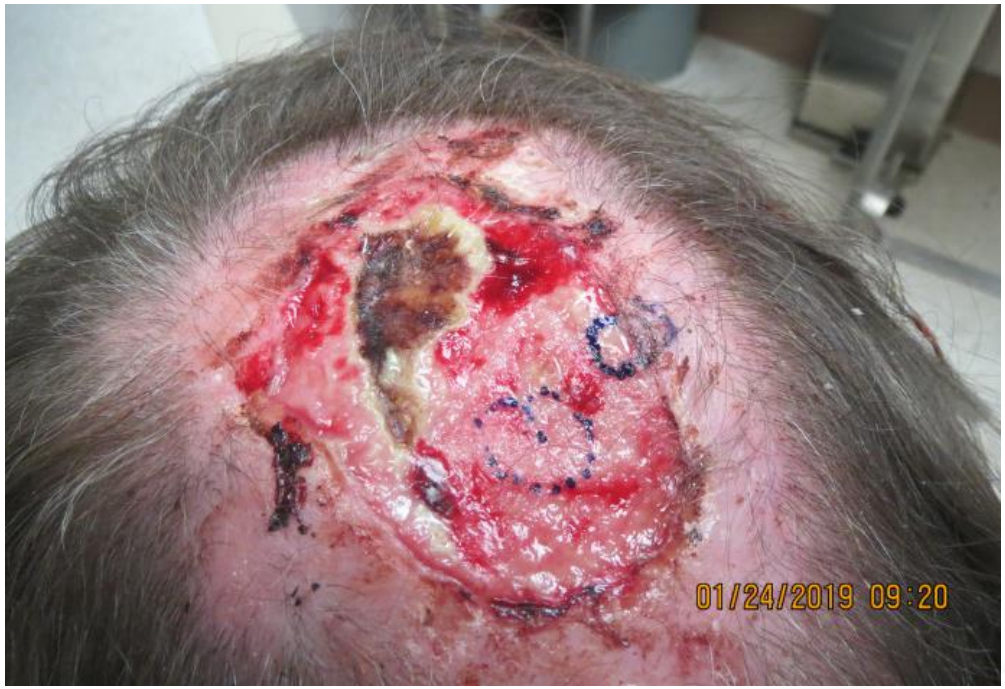
- I have no conflicts of interest to declare.

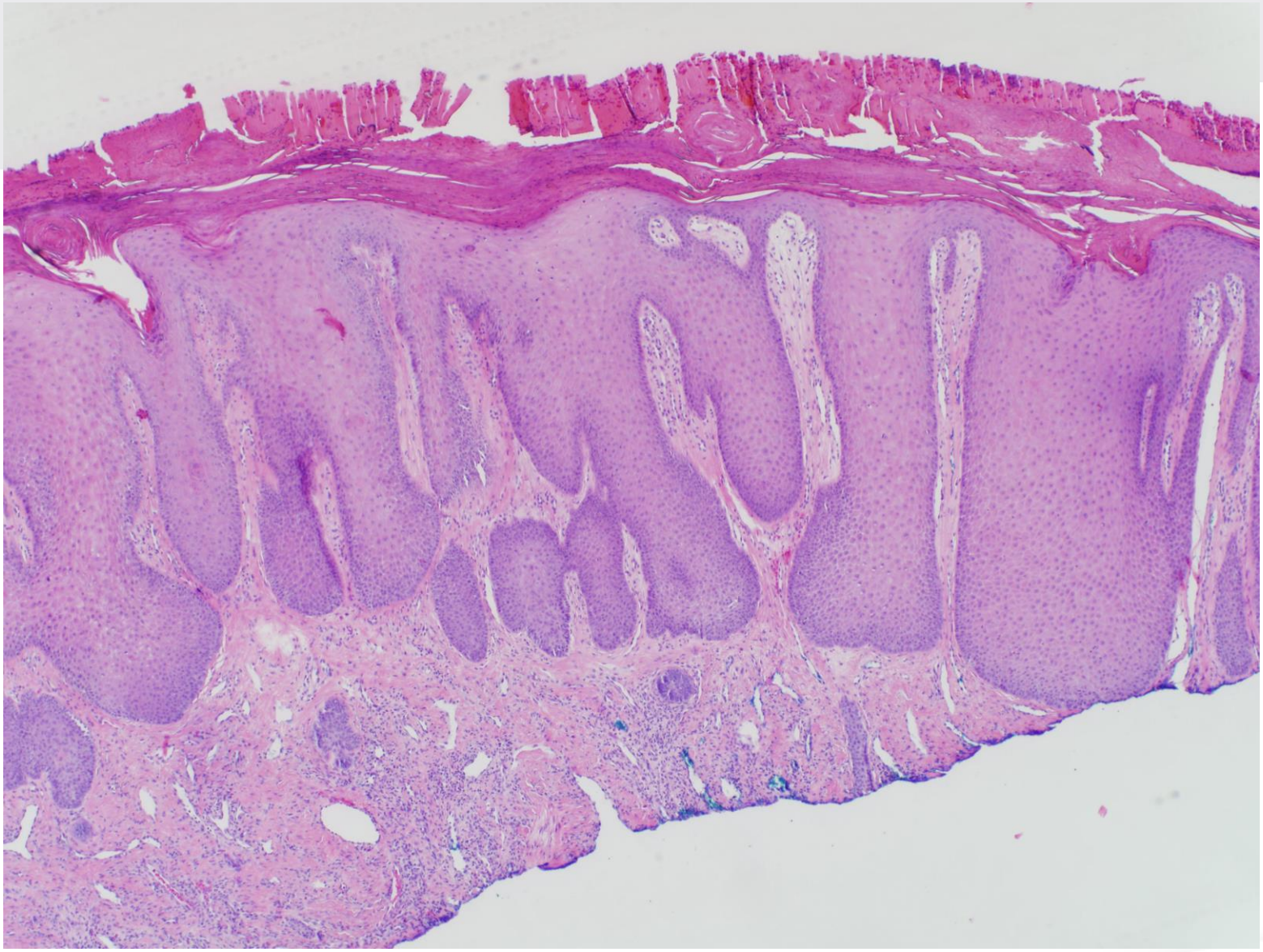
Goals and Objectives

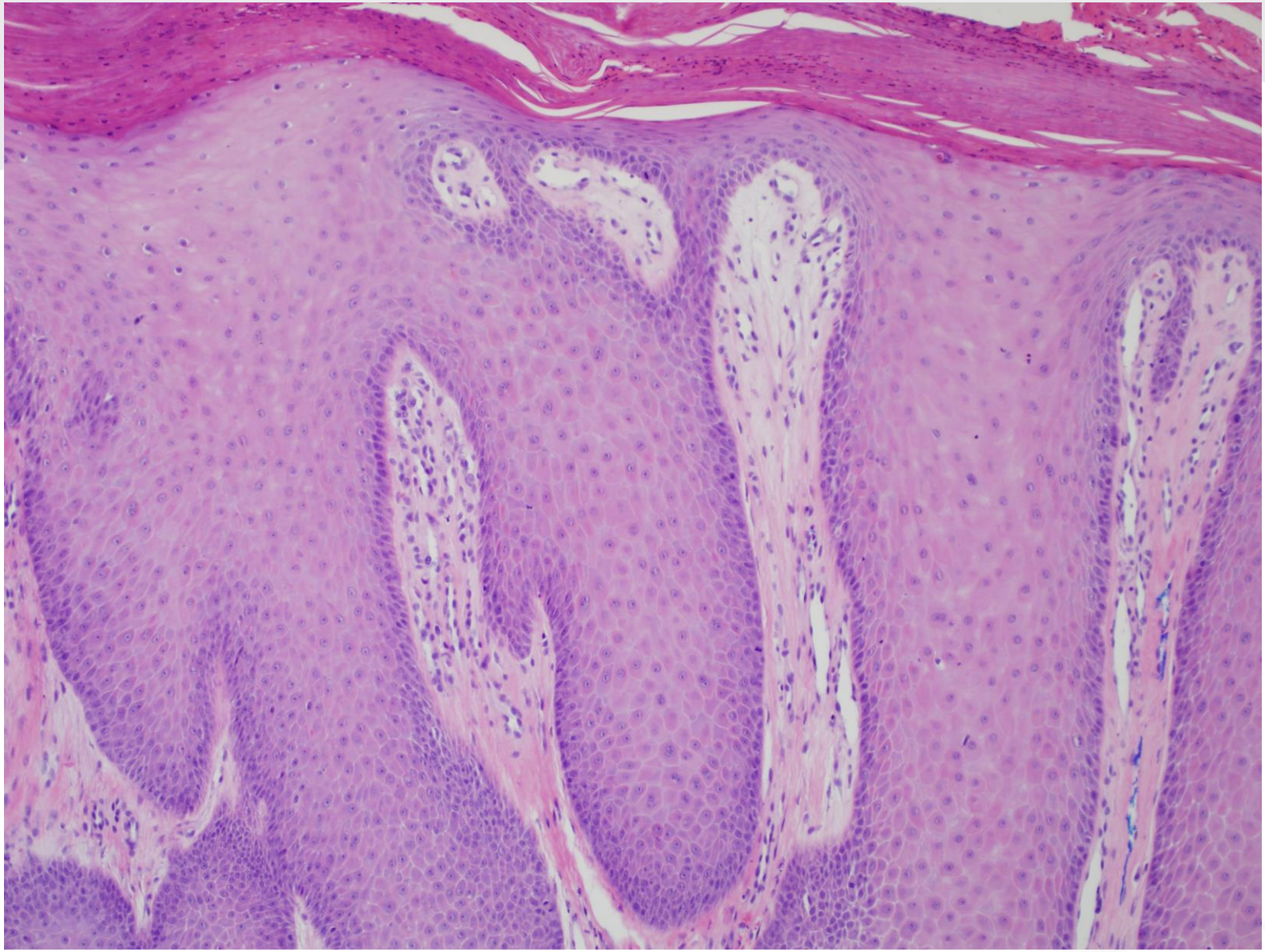
- Appreciate the ramifications of overdiagnosis
- Review a number of conditions that may mimic malignancy
  - Raise awareness of certain less common entities
- Highlight clues to avoid the pitfalls of overdiagnosis

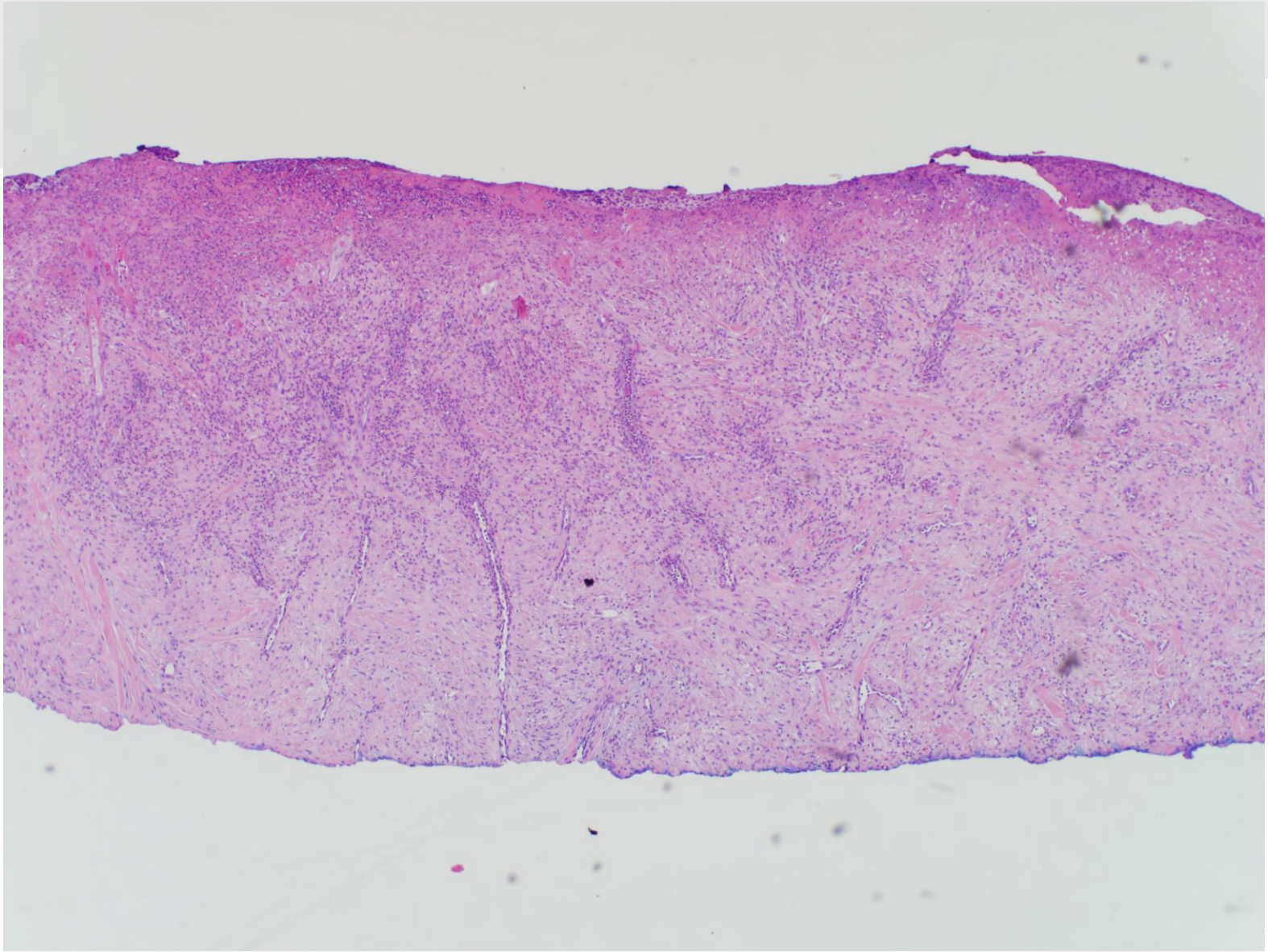
Case Presentation

- 60 y/o male presented to dermatology clinic 1/2019
- He complained of a non-healing sore on his scalp for ~3-4 months
- Denied systemic symptoms, exam failed to reveal other suspicious lesions or lymphadenopathy



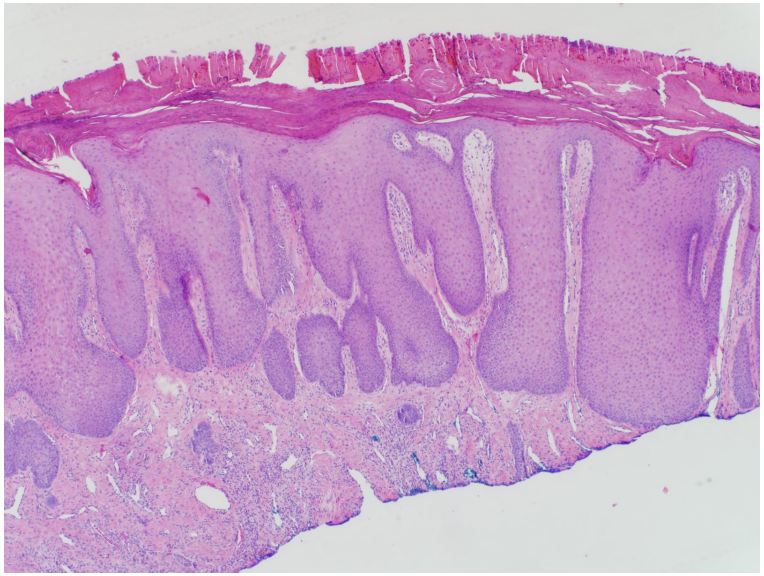


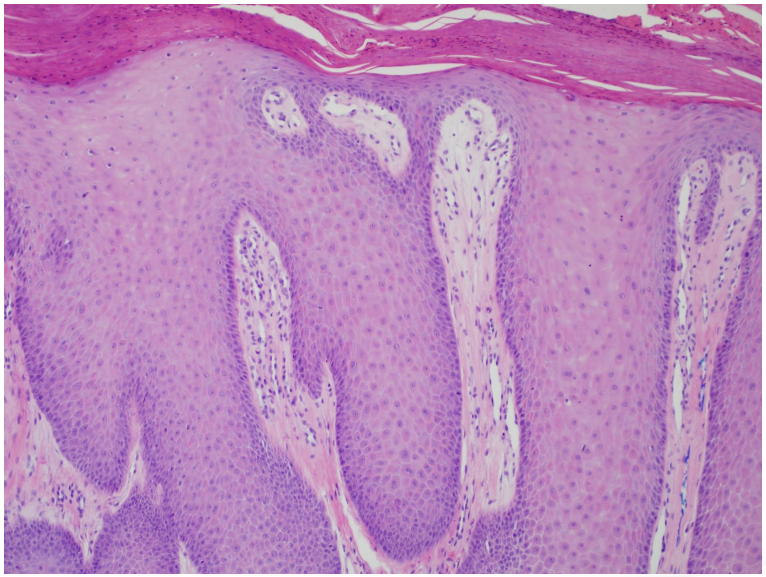




Original pathology report

- 1/23/19:
  - INVASIVE SQUAMOUS CELL CARCINOMA, WELL-DIFFERENTIATED, EXTENDING TO THE BASE OF ONE TISSUE FRAGMENT



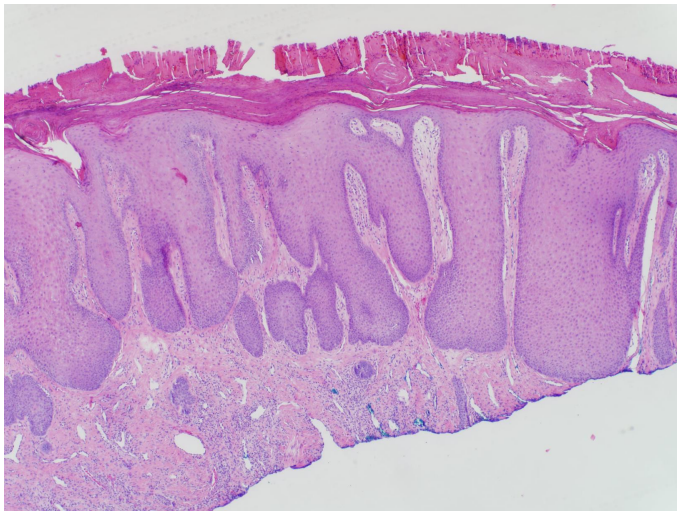


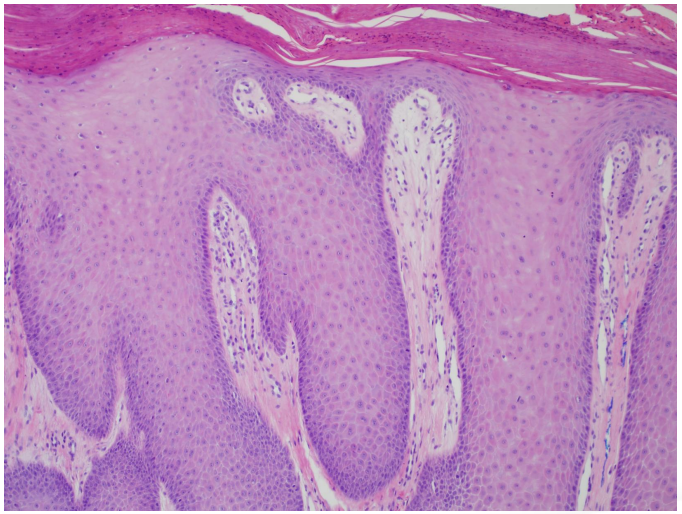
Treatment Course

- Imaging Studies performed:
  - CT Neck Impression: Multiple prominent round cervical lymph nodes including lobular grouped right level II lymph nodes measuring up to 1.2 x 1.2cm total dimension. These cervical nodes are nonspecific, but concerning for metastases in the work-up of patient's scalp vertex lesion.
  - CT Brain: Unremarkable
- Referred to head and neck surgical oncology
- In the OR under general anesthesia patient underwent wide local excision of the lesion, measuring 9 x 7cm with an outer table craniotomy given concern for superficial bony involvement
  - Sentinel lymph node sampling of bilateral cervical nodes performed
  - Integra graft placed
- Pathology report of excision specimen showed no evidence of residual carcinoma and 13 lymph nodes, all negative for carcinoma

Treatment Course

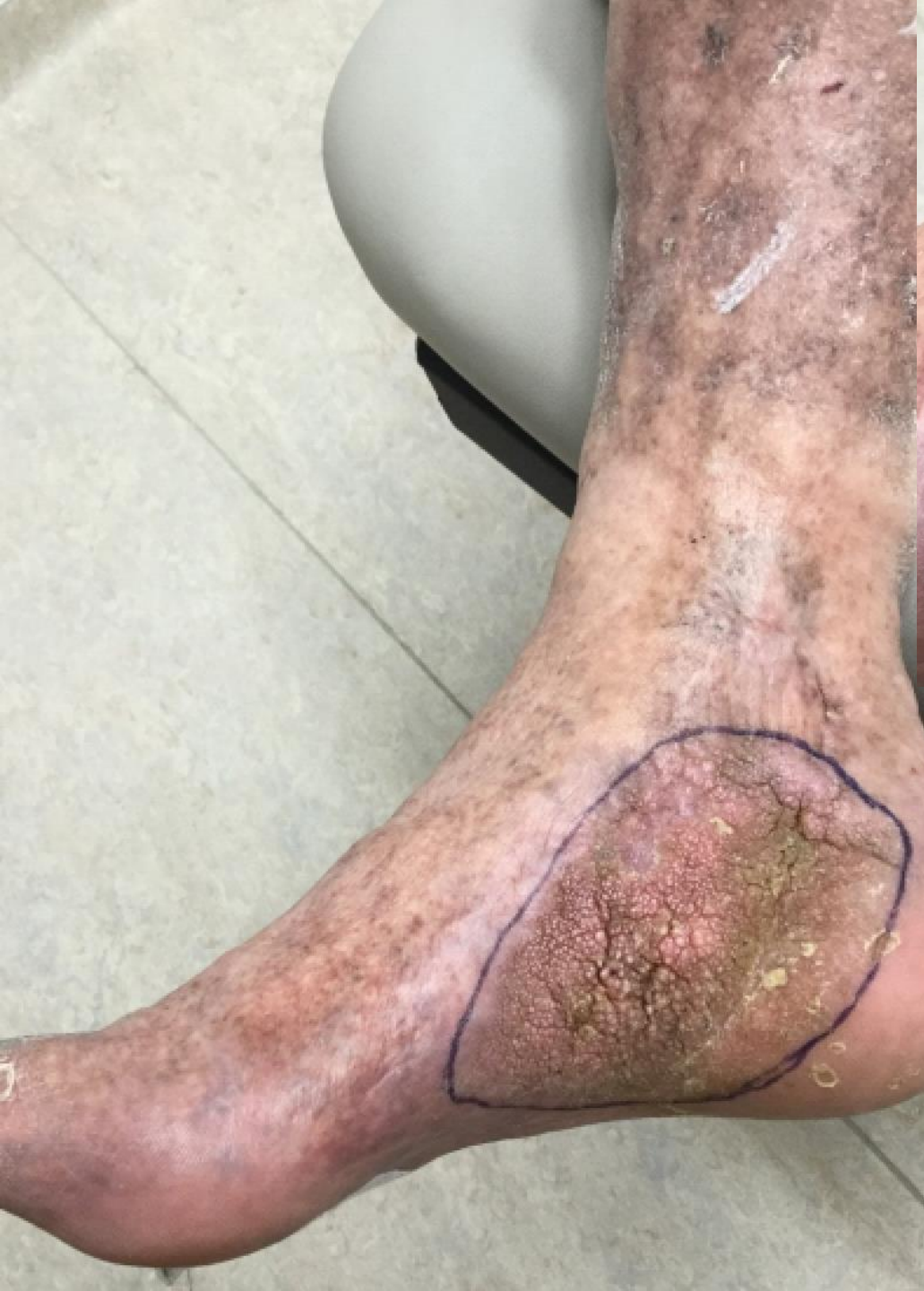
- Pathology review 4/2019 led to re-examination of original specimen with a new rendered diagnosis: PRURIGO NODULARIS, ULCERATED.
- Patient's last follow-up was 06/2019 at which time he still had a large, healing open wound on his scalp

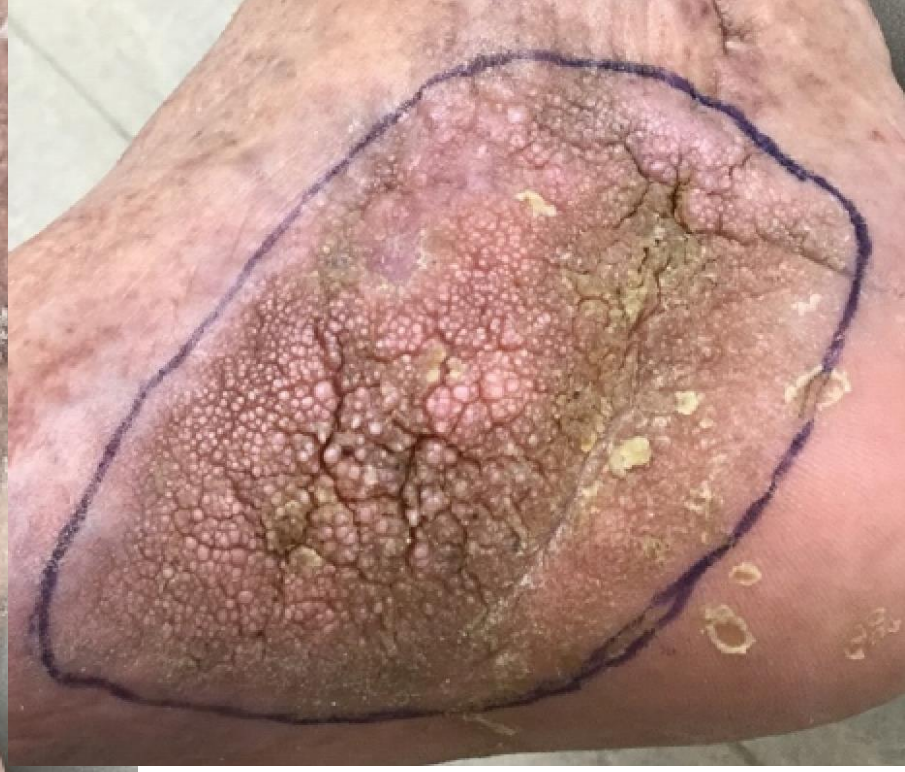




Case Presentation

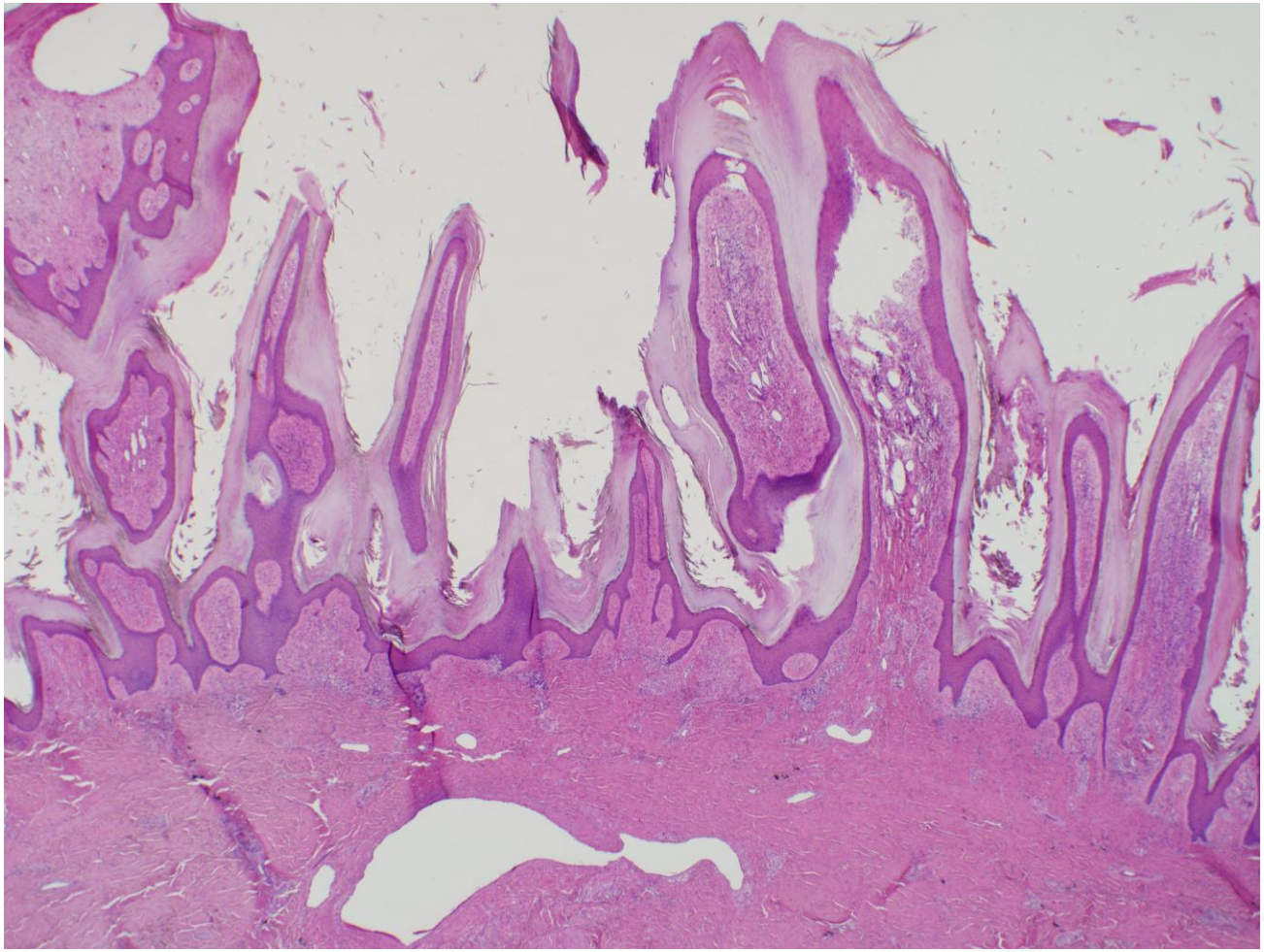
- 64 y/o male presented with a slow-growing mass on the instep of his right insole, present for 6 months
- Patient also complained of an “itchy, flaky rash” on his right leg and trunk
- Outside biopsy was obtained and interpreted as verrucous carcinoma
- Patient was referred to the University of Utah healthcare system
- Past Medical History:
  - History of multiple surgical procedures on the right lower extremity following trauma
  - history of blood clots, unclear physical location
  - Diabetes
  - Hypertension
- Social History:
  - Current everyday smoker





- 15 x 7cm verrucous plaque on the right foot
- Right leg showed evidence of scarring from prior trauma and previous procedures including 5th digit amputation

Upon Re-excision



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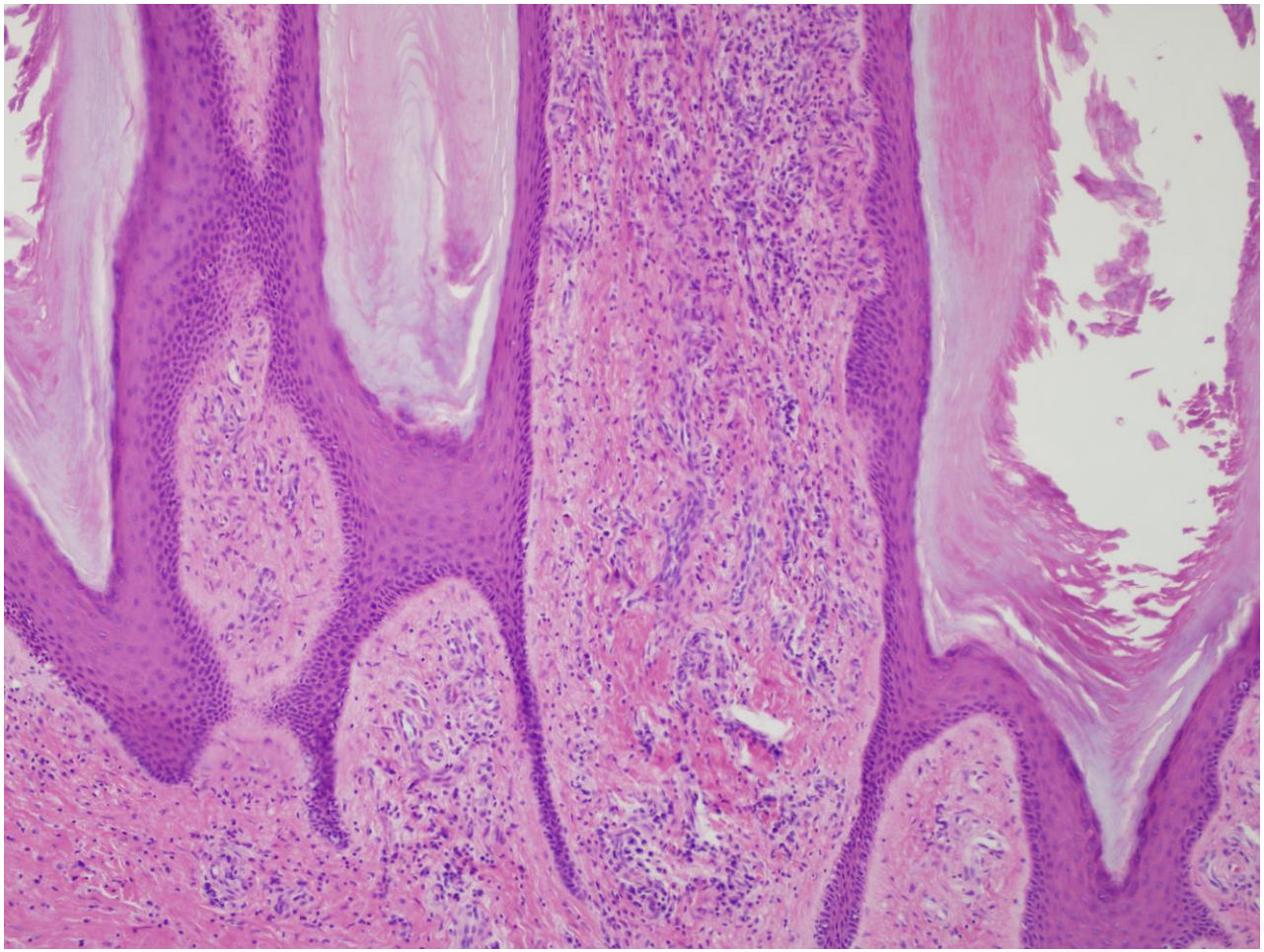

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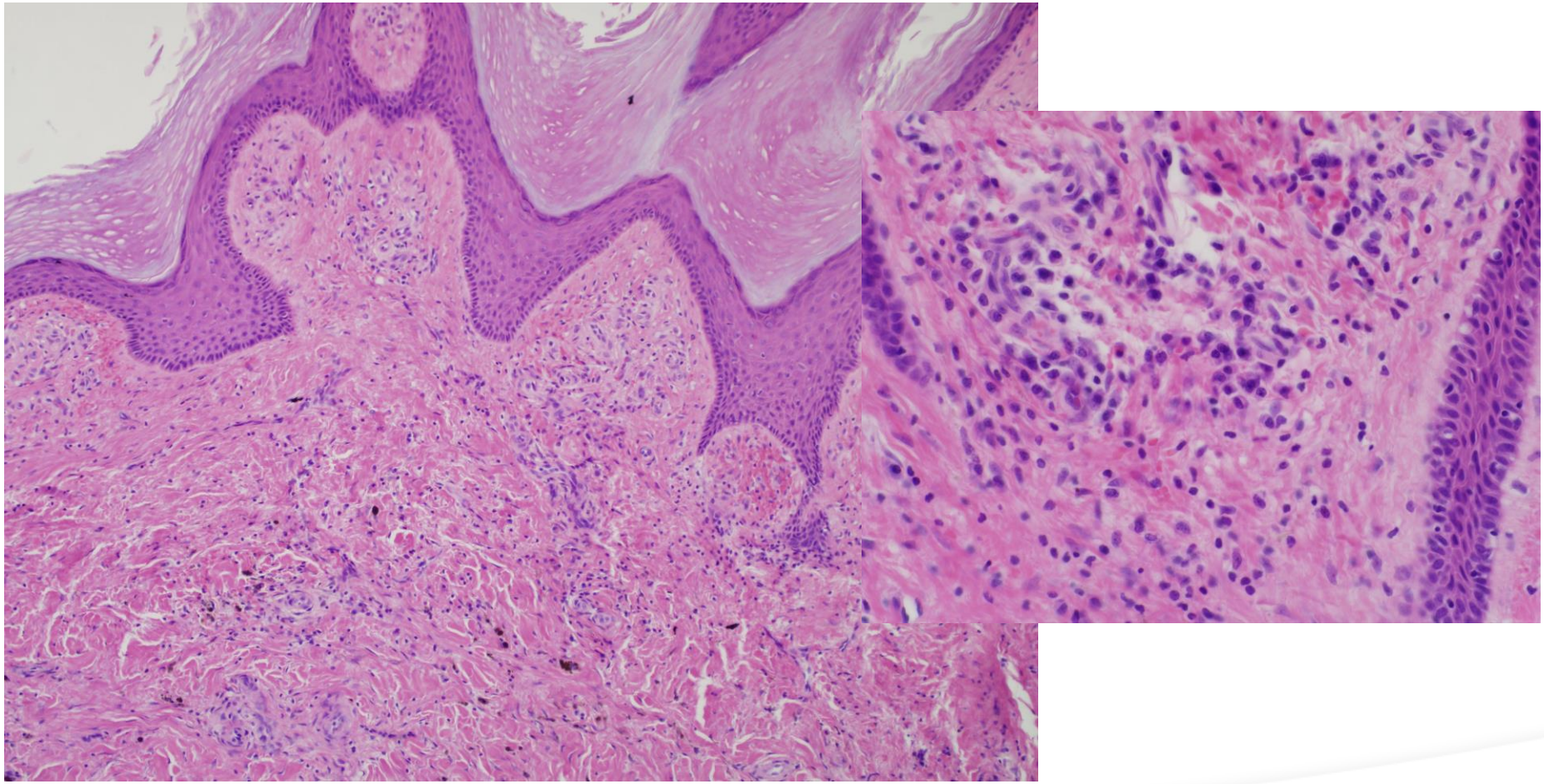
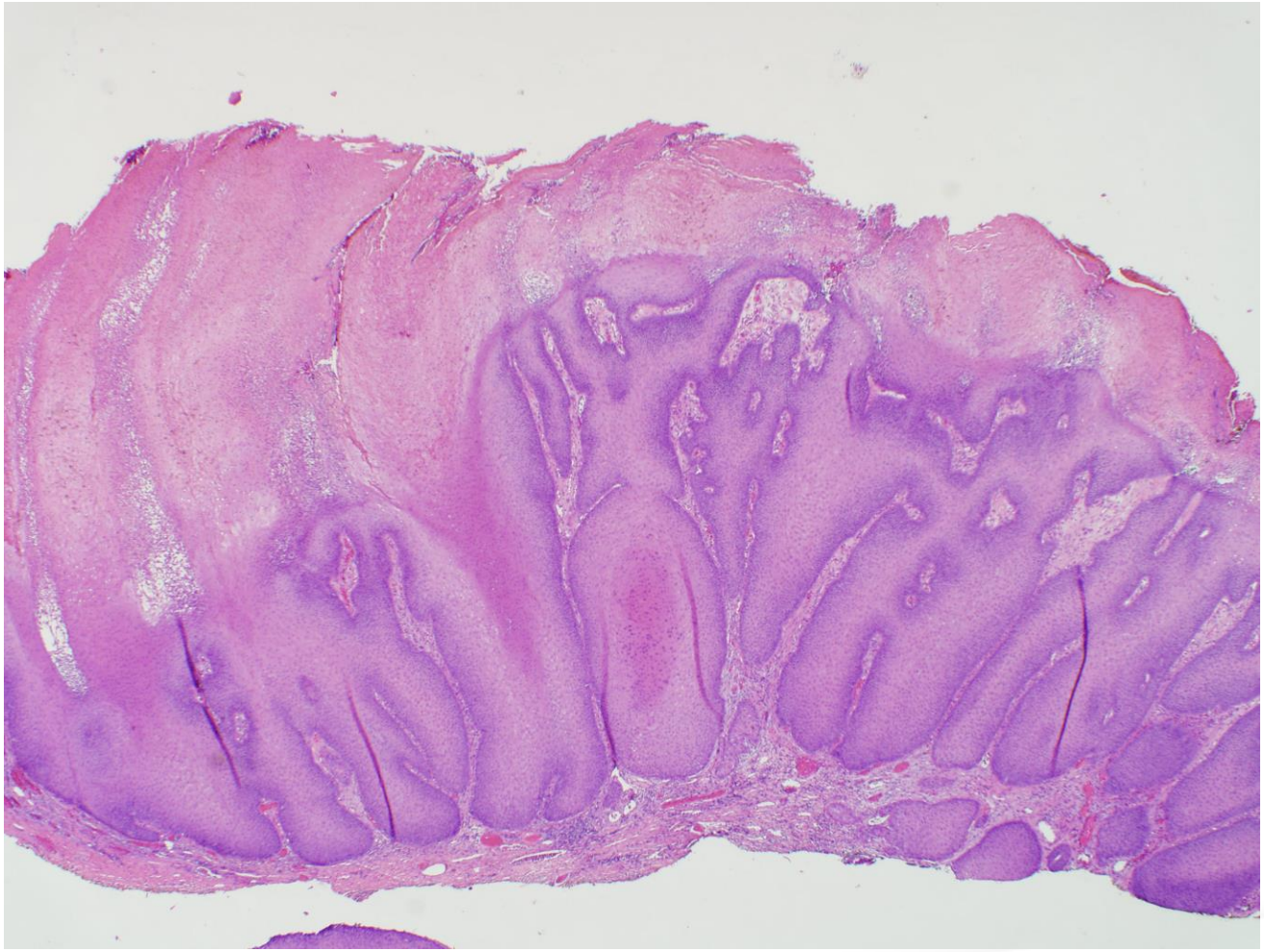


Procedure Follow-up

- Pt required a split thickness skin graft taken from his thigh measuring 9 x 12cm after confirmation of clear margins.
- Pt underwent general anesthesia on two separate occasions and had difficulty recovering from his first procedure with increased oxygen requirements and difficulty ambulating
- Detailed documentation lacking, but patient was prescribed Bactrim 1 month following procedure

Verrucous Carcinoma



Overdiagnosis

- **Overdiagnosis**: “When individuals are diagnosed with conditions that will never cause symptoms or death”
- **Why?**
  - Fear of undertreatment is greater than fear of overtreatment – may lead to lowering thresholds
    - Also an issue in the fields of breast, prostate, and thyroid cancer
  - Aversion/fear of legal problems
  - Uncertainty
    - Lack of clear disease definitions

Med Health Care Philos. 2017 Jun;20(2):269-280. doi: 10.1007/s11019-016-9748-8.

Defining disease in the context of overdiagnosis.

Walker MJ[1], Rogers W[2].

Overdiagnosis – Why?

- Disease: dysfunction that has a significant risk of causing harm to the patient
  - Easier to diagnose “disease” when strict criteria and definitions of disease are in place
  - These strict criteria are missing in many dermatologic conditions
- Pathologists often disagree WITH THEMSELVES (!) when reviewing cases separated by extended time periods
  - Recent study examined the reproducibility of diagnosis in melanocytic neoplasms by 187 pathologists
  - Slides were examined by the same pathologist on two separate occasions at least 8 months apart
  - Diagnoses spanning moderately dysplastic nevi to early stage invasive melanoma were neither reproducible nor accurate

Pathologists' diagnosis of **invasive melanoma** and melanocytic proliferations: observer accuracy and reproducibility study.
Elmore JG, Barnhill RL, Elder DE, Longton GM, Pepe MS, Reisch LM, Carney PA, Titus LJ, Nelson HD, Onega T, Tosteson ANA, Weinstock MA, Knezevich SR, Piepkorn MW.
BMJ. 2017 Jun 28;357:j2813. doi: 10.1136/bmj.j2813. Erratum in: BMJ. 2017 Aug 8;358:j3798.

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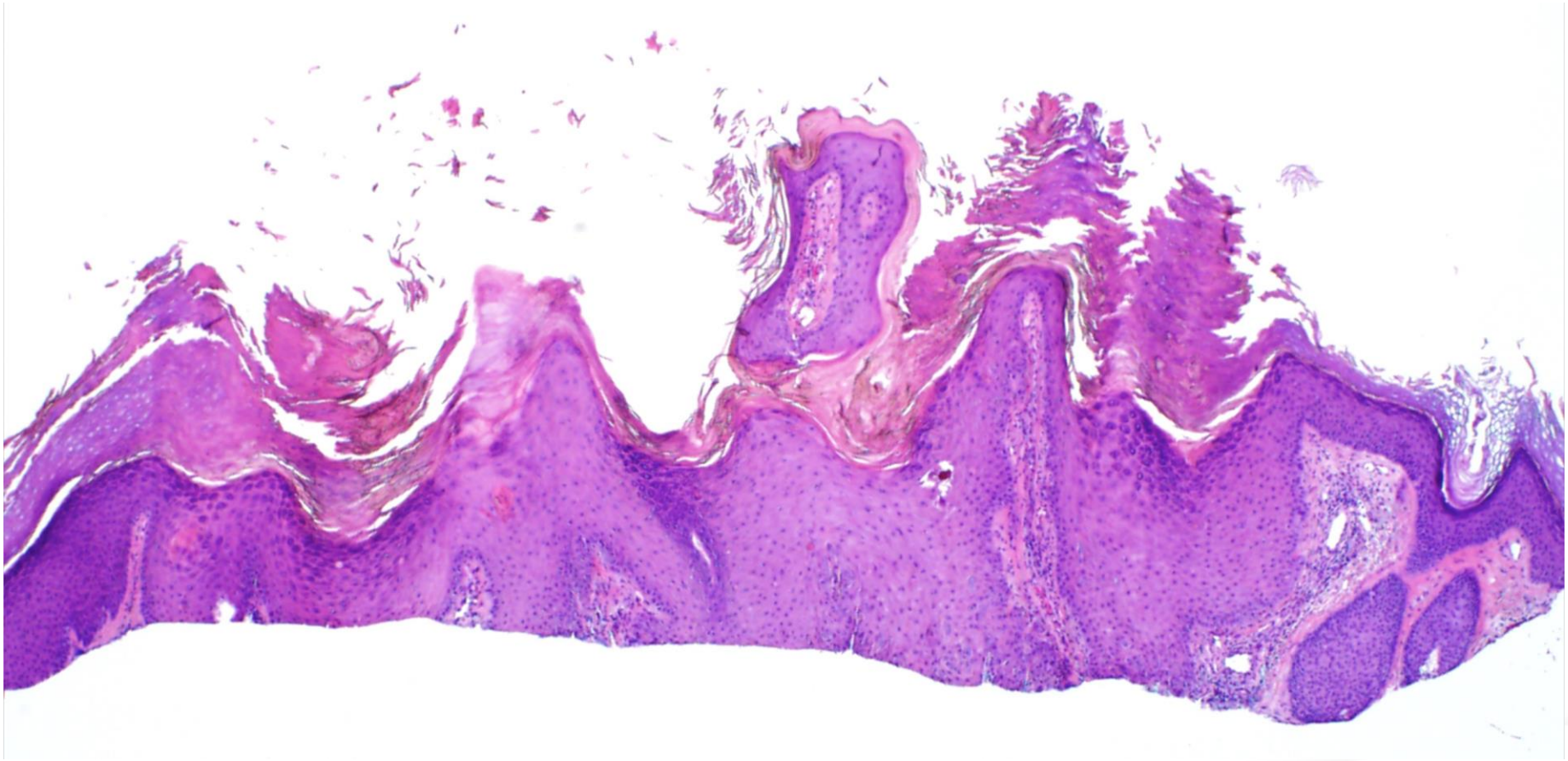
Differentiating reactive squamous atypia from carcinoma



Differentiating reactive squamous atypia from carcinoma

- My daily dilemmas:
  - Superficially transected inflamed squamous proliferations
    - Carcinoma?
    - Keratoacanthoma?
    - Lichenoid keratosis?
    - The top of an underlying, incompletely sampled process?
  - Lichenoid actinic keratosis versus benign lichenoid keratosis
  - Inflamed verruca versus squamous cell carcinoma in situ

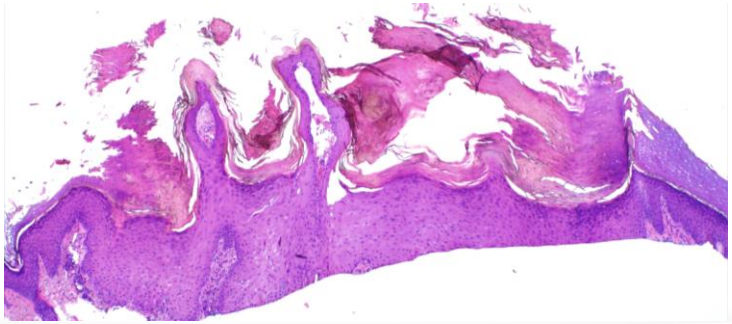


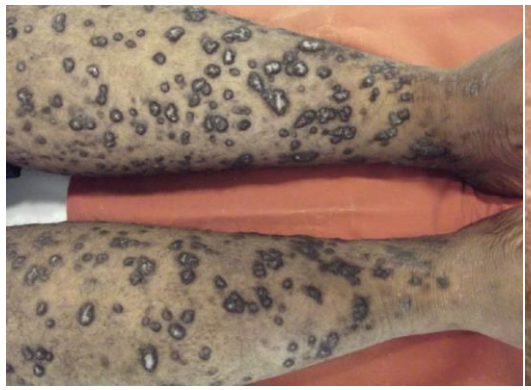
TABLE 1. Disorders Associated With PEH

Category	Reference(s)
Infections	
Mycobacterial	
M. marinum	2
M. tuberculosis	3
Leprosy	4–6
Deep fungal	
Blastomycosis	7,8
Paracoccidioidomycosis	7,9,10
Sporotrichosis	7,11
Chromomycosis (chromoblastomycosis)	7,12–15
Coccidioidomycosis	16
Aspergillus	17,18
Viral	
Genital and perianal herpes simplex in patients with AIDS	19
Chronic verrucous varicella zoster virus infection in patients with AIDS	20,21
Bacterial	
Blastomycosis-like pyoderma	22–24
Bacillary angiomatosis	25
Actinomycosis	26
Granuloma inguinale	27
Osteomyelitis	28,29
Protozoal	
Leishmaniasis	30
Spirochetal	
Gumma	27
Neoplastic conditions	
Basal cell carcinoma	31
Lymphoproliferative disorders	—
Nasal NK/T lymphoma	32,33
Anaplastic Large Cell Lymphoma	34–40
Mycosis fungoides	35
Lymphomatoid papulosis	37,39,41
Granular cell tumor	42,43
Melanoma	44–47
Spitz nevus	48–50
Chronic inflammation/irritation	
Prurigo nodularis	51
Halogenodermas	52–57
Hypertrophic lupus erythematosus	58–66
Hypertrophic lichen planus	67
Perianal pseudoverrucous papules and nodules in children	68
Elephantiasis nostras verrucosa	69
Chronic cutaneous wounds	70
Chondrodermatitis nodularis helicis	71
Lichen sclerosus	72
Malakoplakia	73
Pyodermatitis–pyostomatitis vegetans	74
Pemphigus vegetans and pemphigoid vegetans	75–83
Miscellaneous	
Tattoo	84–86
After Mohs surgery	87,88

Zayour M, Lazova R.
Am J Dermatopathol. 2011 Apr;33(2):112-22; quiz 123-6. doi: 10.1097/DAD.0b013e3181fcfb47. **Review**.

Reactive squamous atypia/pseudoepitheliomatous hyperplasia (PEH) versus malignancy

- An issue when:
  - Biopsy is small and superficial, lesion is only partially sampled
- Clinical history is not provided
  - Are there multiple lesions?
  - Does the patient have known systemic conditions? (e.g.. lupus, lichen planus)
  - History of trauma?
  - History of travel?



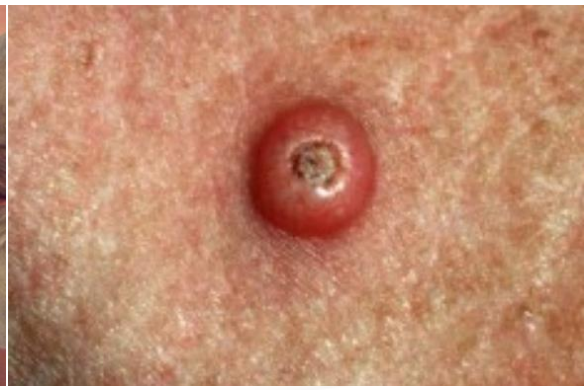
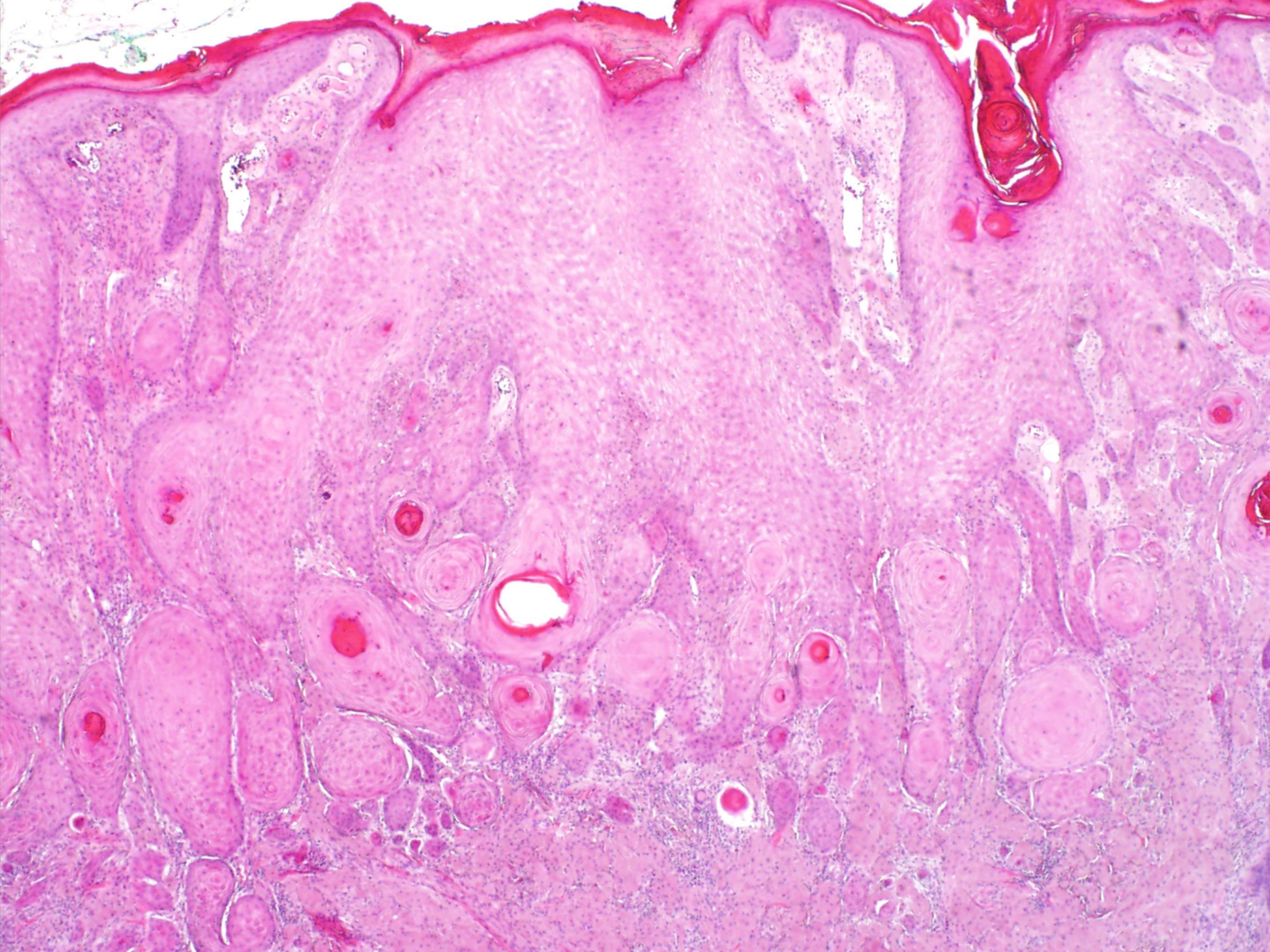
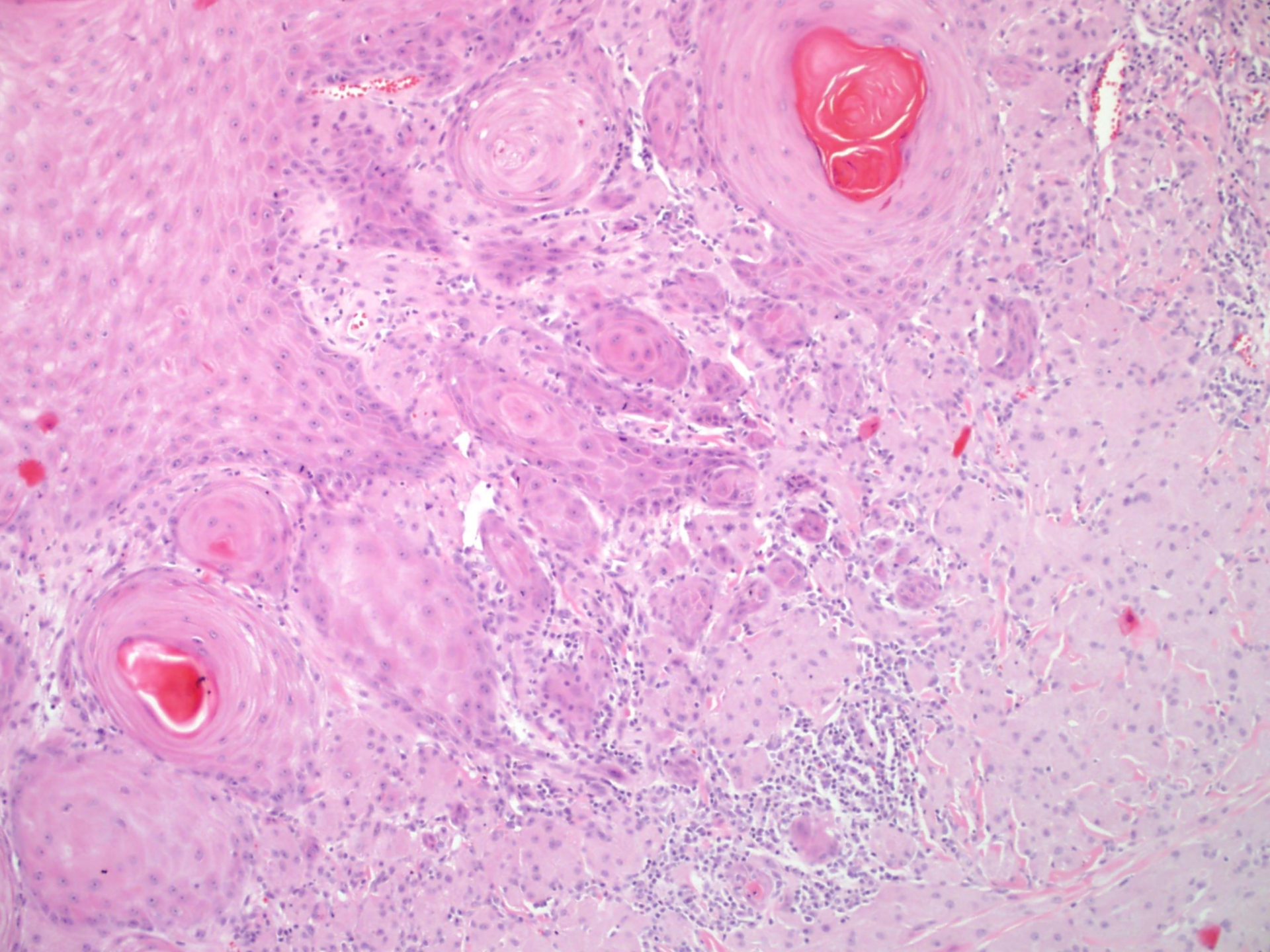
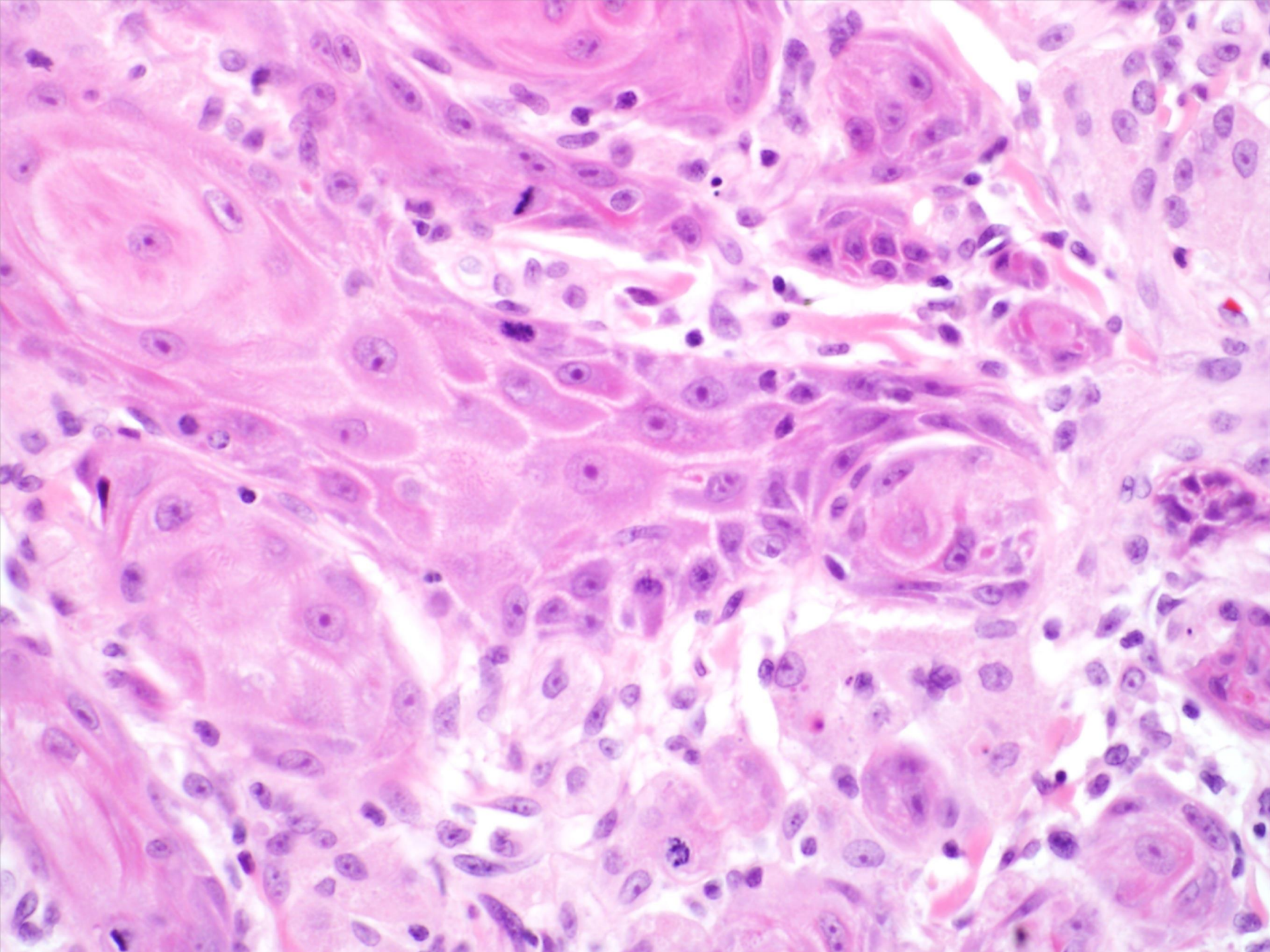


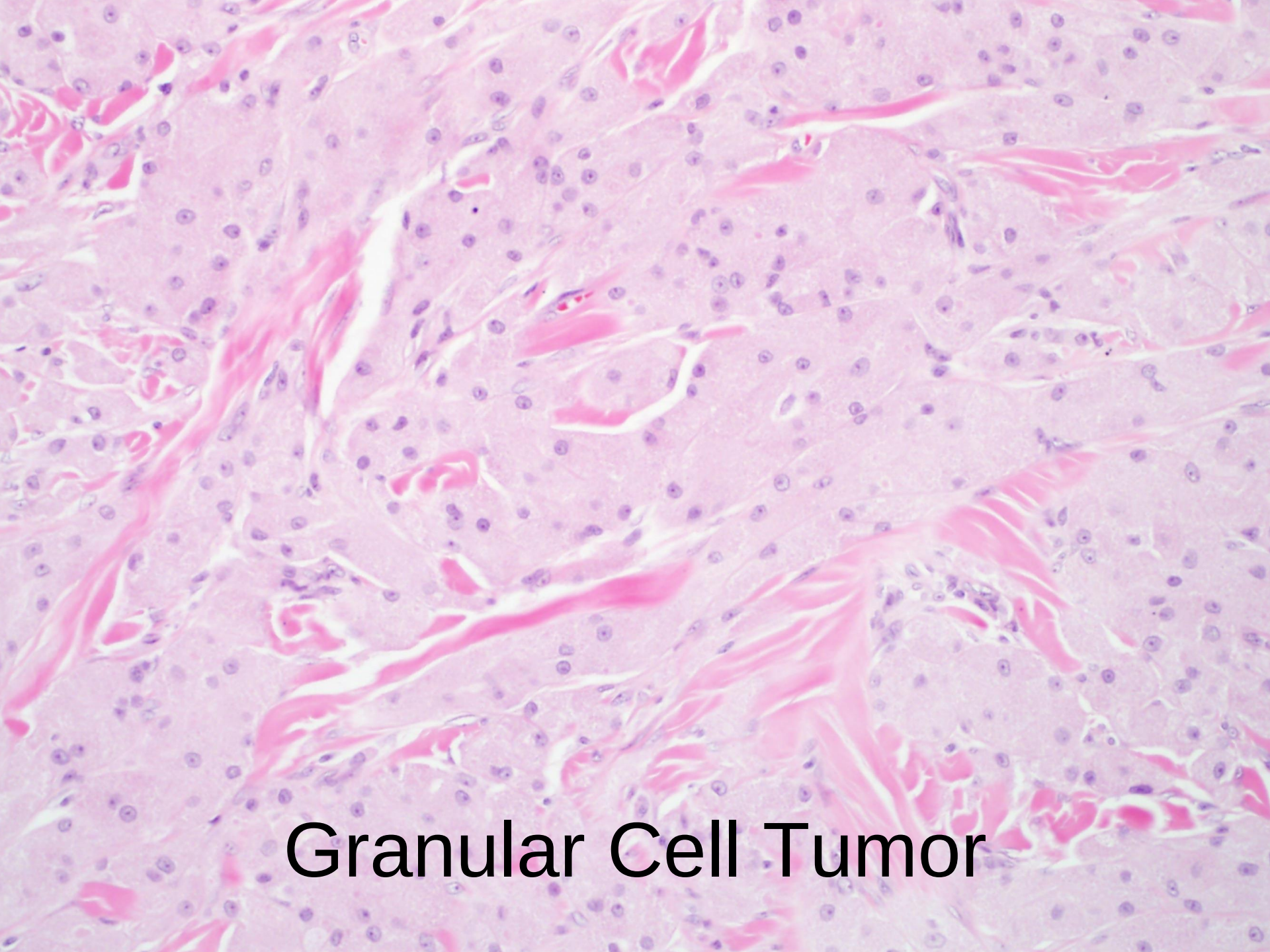
Photo Credits: https://skincheck.com.au/skinclinic/keratoacanthoma/

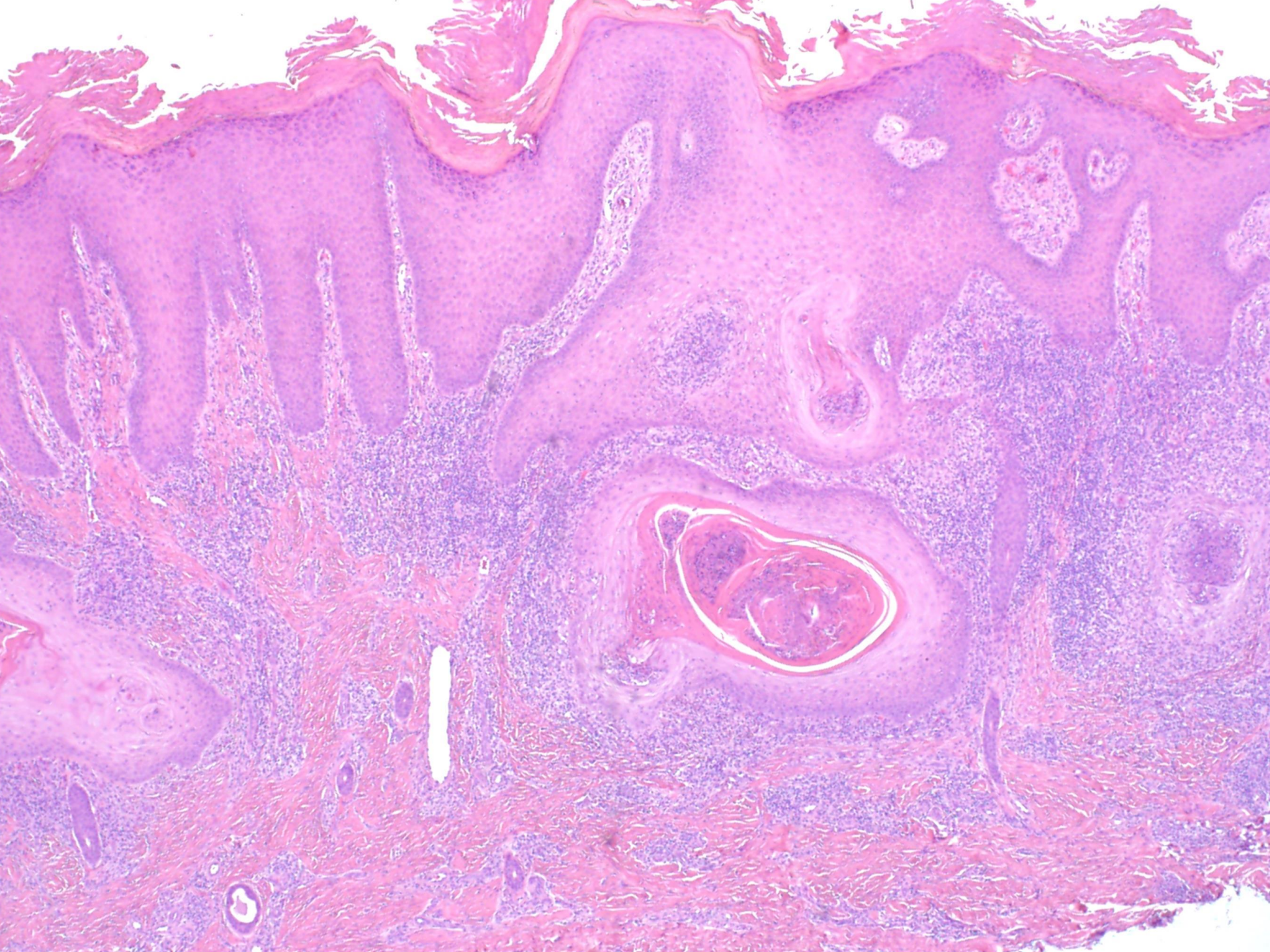
Gutte RM. Acitretin: A good treatment option for hypertrophic lichen planus. Indian J Drugs Dermatol 2016;2:28-30

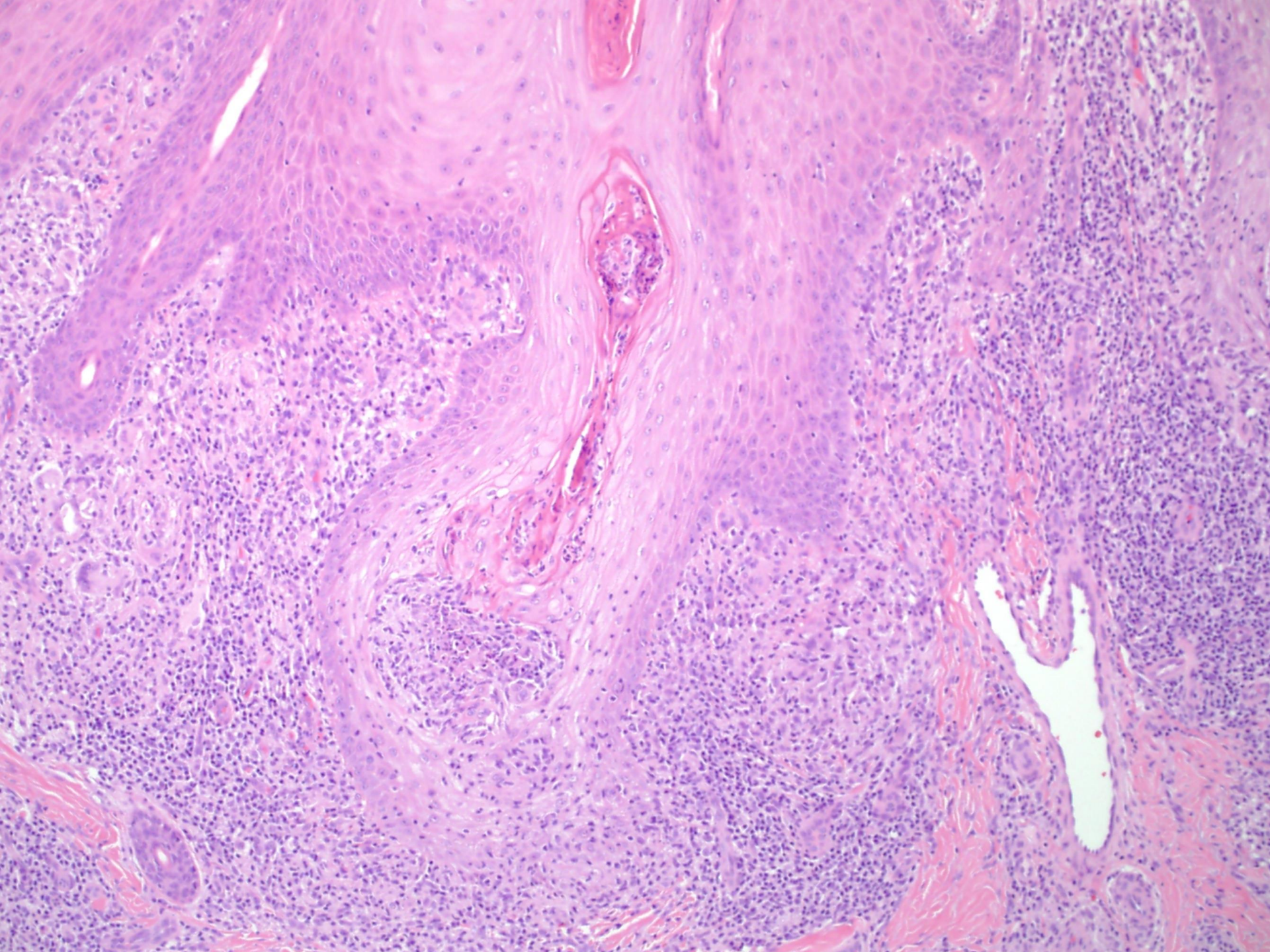


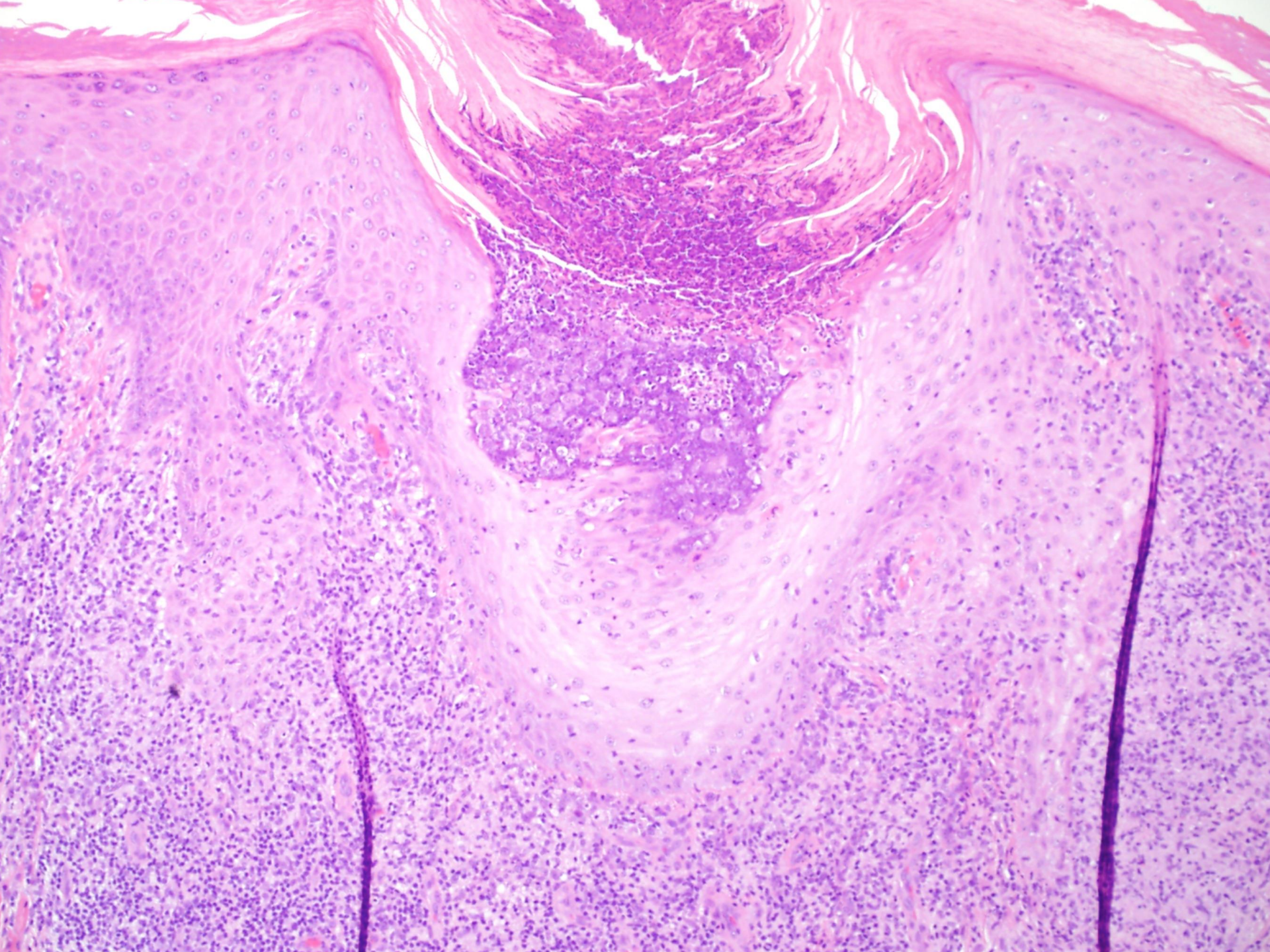


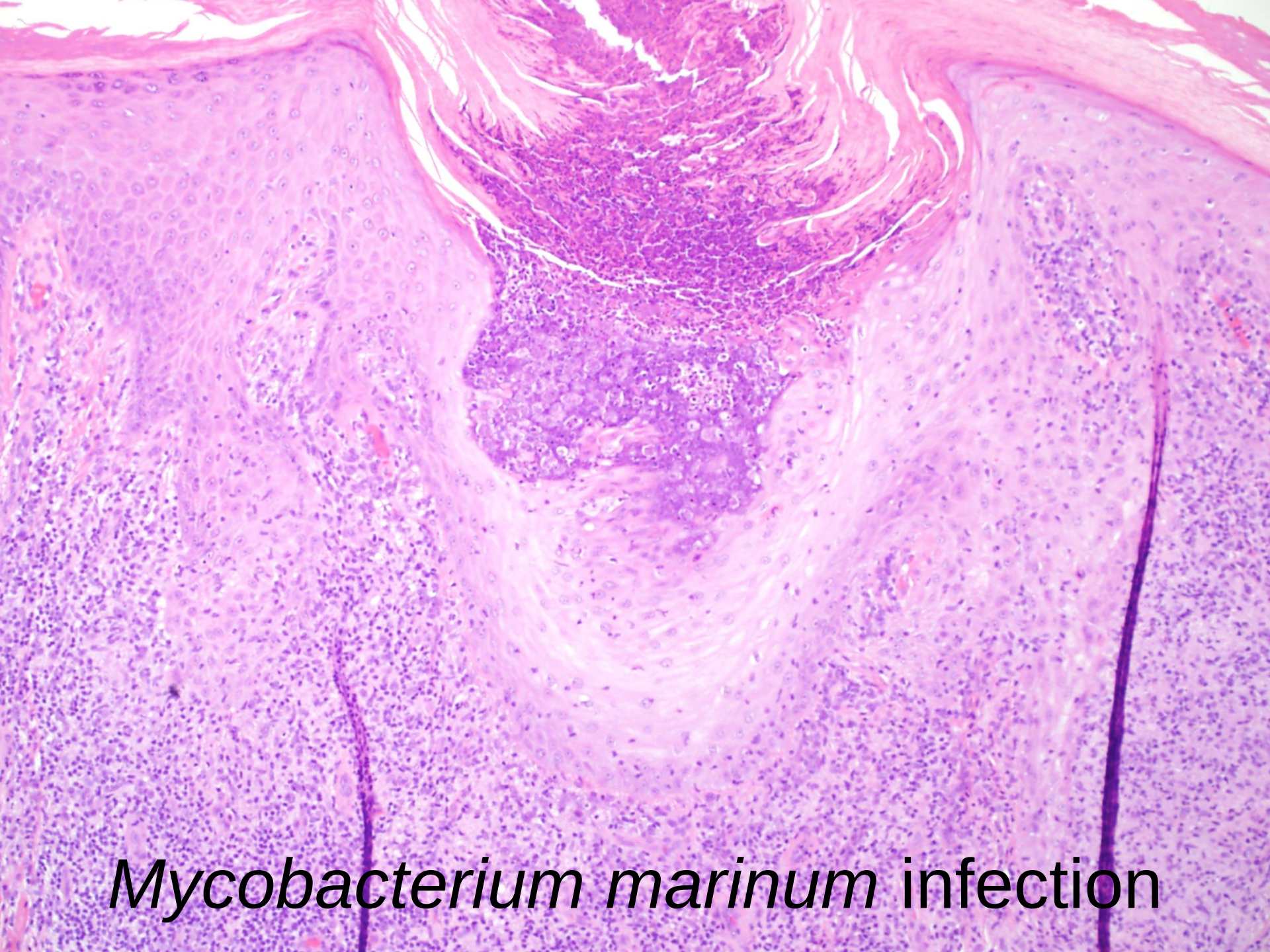


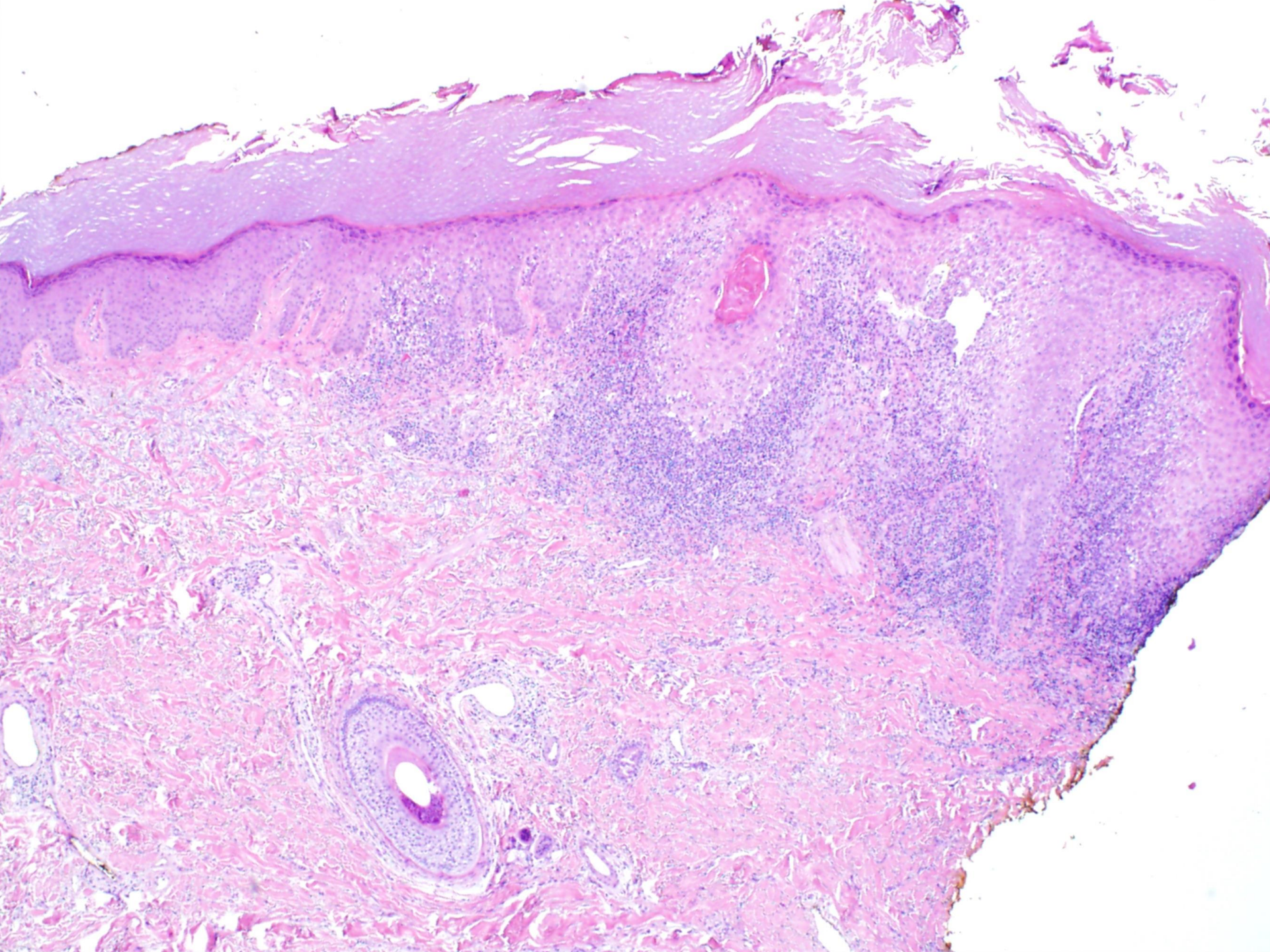

Granular Cell Tumor

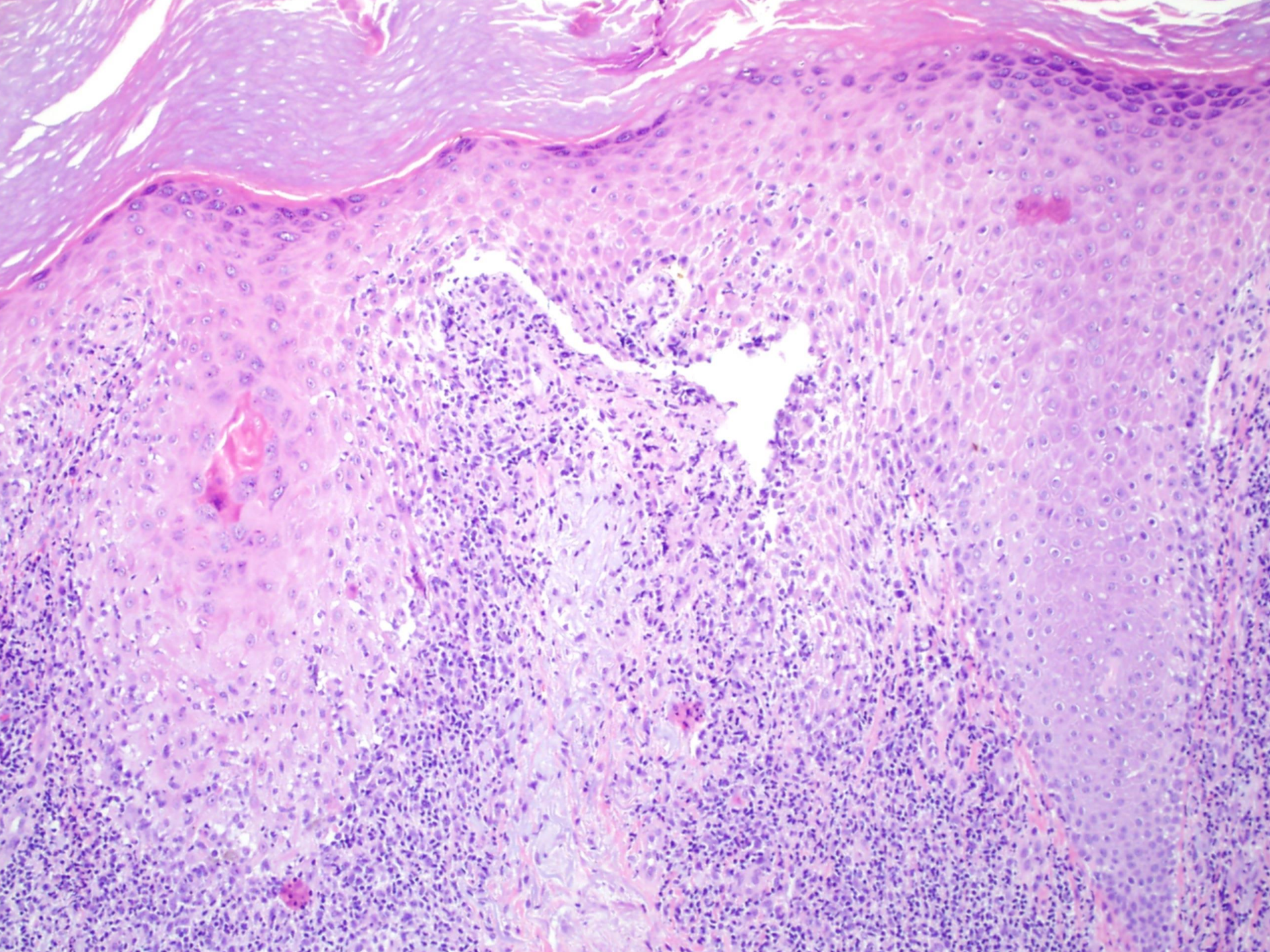







Mycobacterium marinum infection





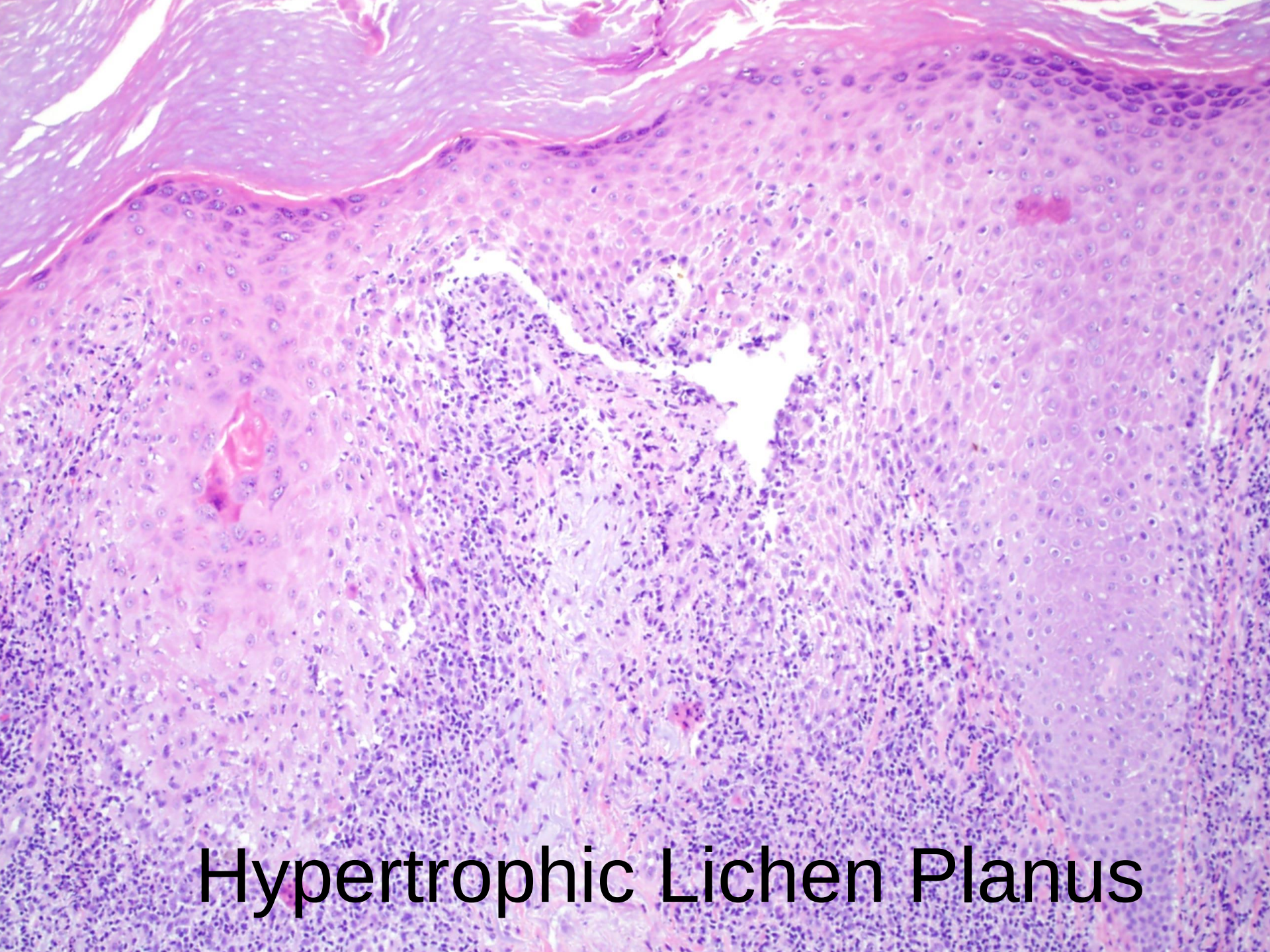

Hypertrophic Lichen Planus

TABLE 2. Histopathologic Features Differentiating PEH from SCC

Feature	PEH	SCC
Aggregates of proliferating keratinocytes	Derived essentially from adnexal epithelium	Mostly of epidermal origin
Peripheral border of epithelial hyperplasia	Jagged with sharply pointed base, usually within upper to mid reticular dermis	Bulbous, irregularly shaped, and/or infiltrative; often with surrounding dermal fibrosis; may extend into subcutaneous fat
Stratum corneum	Ortho- or parakeratosis	Parakeratosis common
Stratum granulosum	Normal to increased	Decreased
Keratin pearl formation	Common	Variable
Cytologic atypia	Minimal; usually located in the basal layer	Variable; sometimes a focus of actinic keratosis or SCC in situ in adjacent epidermis
Mitotic activity	Rare; usually in the basal layer; not atypical	Variable; atypical mitoses at all levels of the epidermis
Keratinocyte necrosis	Absent	Variable
Intraepithelial inflammatory cells	Common; mostly neutrophils and eosinophils	Uncommon
Vascular and perineural invasion	Absent	Variable
Underlying dermal pathologic process	Common	Absent

Zayour M, Lazova R.
Am J Dermatopathol. 2011 Apr;33(2):112-22; quiz 123-6. doi: 10.1097/DAD.0b013e3181fcfb47. **Review**.

Difficult squamous lesions – Take home points

- Clinical presentation/history can be crucial
  - Taking the time to call a clinician can save time in the future
- Consider, and rule out mimics prior to diagnosing carcinoma
  - Special stains and/or immunohistochemistry
- It is ok to be non-committal
  - Ask for a deeper biopsy
  - Recommend tissue cultures
  - Better to ask for more tissue than to overdiagnose

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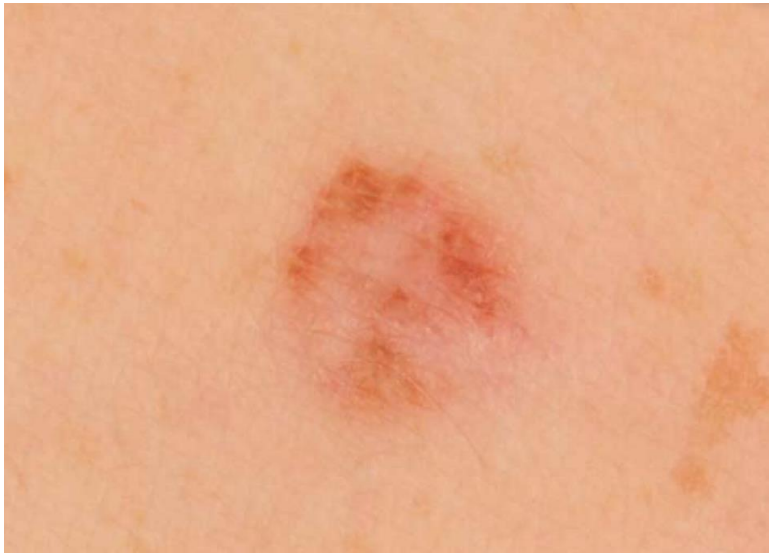
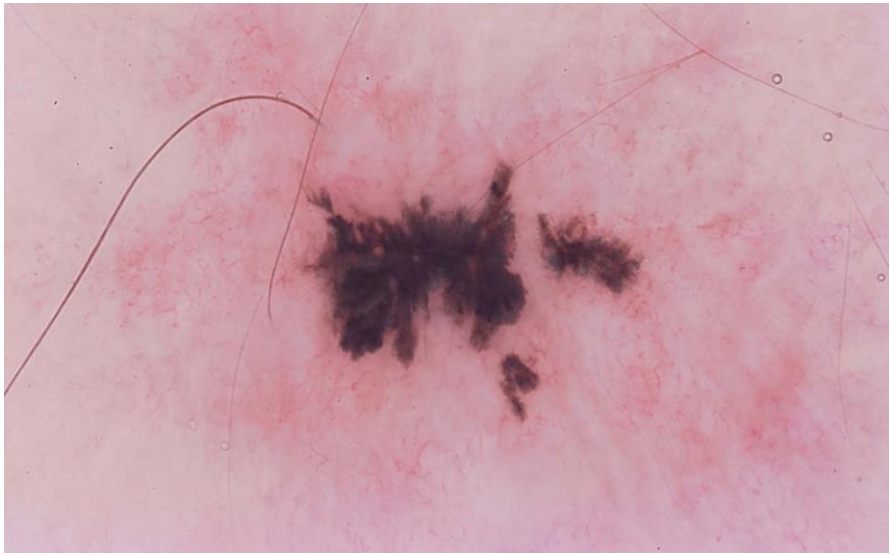
The recurrent nevus, aka "pseudomelanoma"

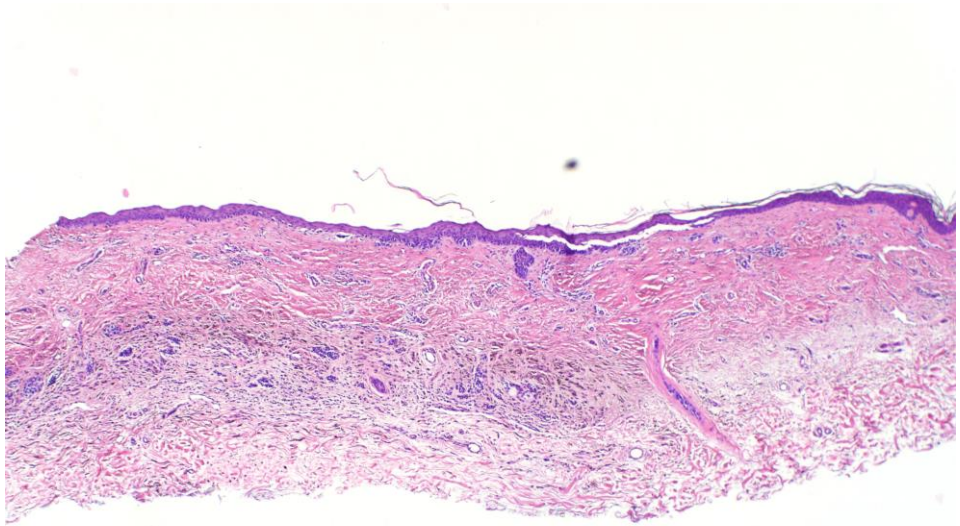
- When a benign melanocytic neoplasm recurs, histologic and clinical features may overlap with melanoma





The recurrent nevus, clues to diagnosis

- At low power, a classic trileveled appearance may be present:
  - Junctional melanocytic proliferation
  - Fibrosis/scar
  - Benign intradermal melanocytic component
- The atypical component of the lesion should be limited to areas above the scar.
  - If the atypical component extends beyond the scar, the diagnosis of recurrent nevus should be reconsidered



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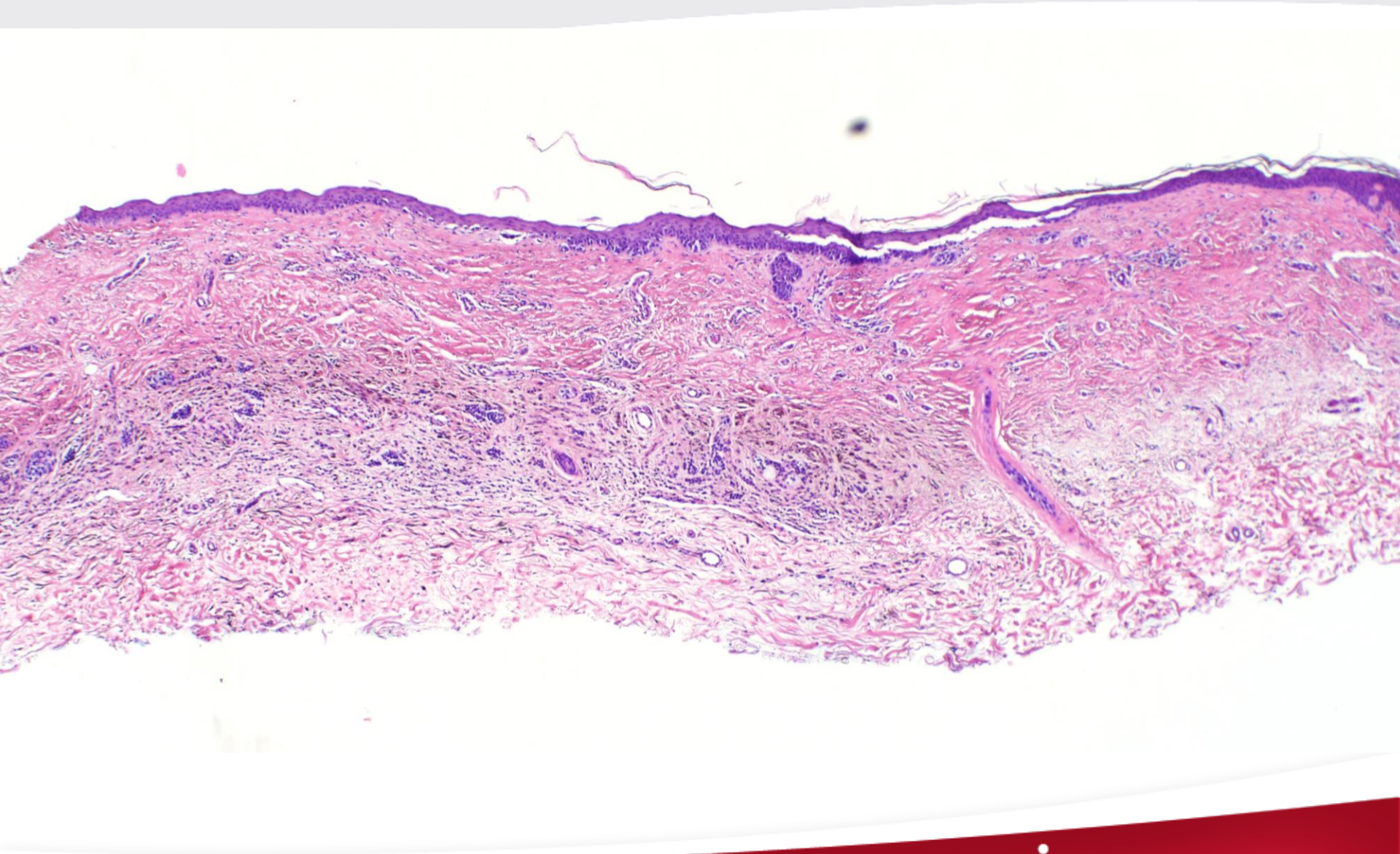
Arch Pathol Lab Med. **2019** Jul;143(7):789-810. doi: 10.5858/arpa.2017-0547-RA. Epub 2018 Jul 30.



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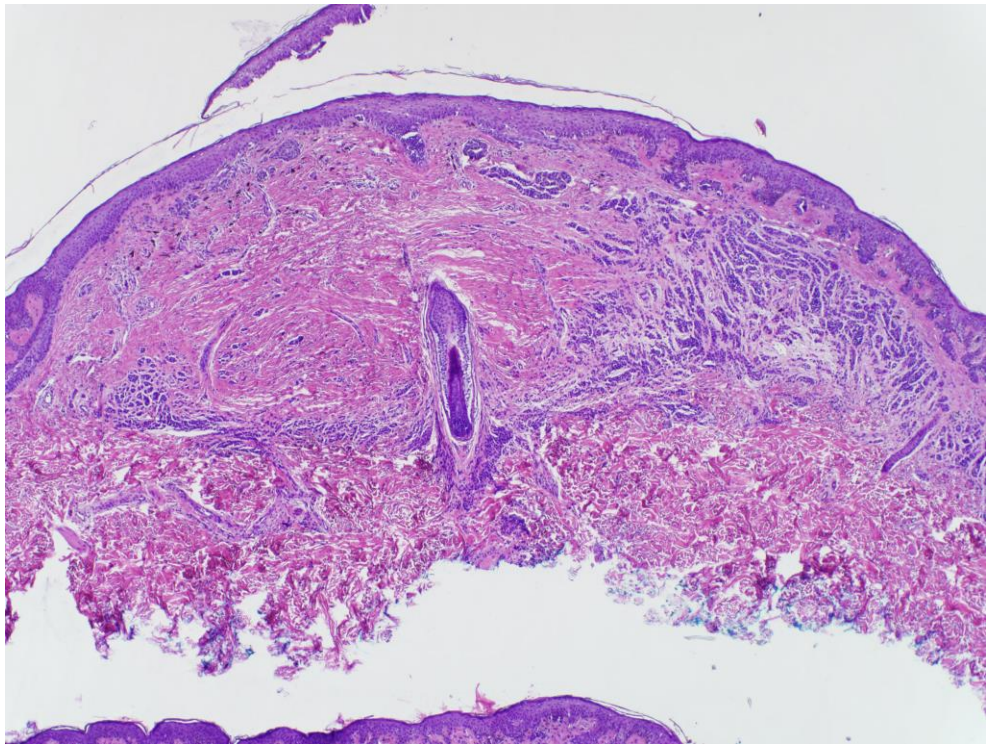

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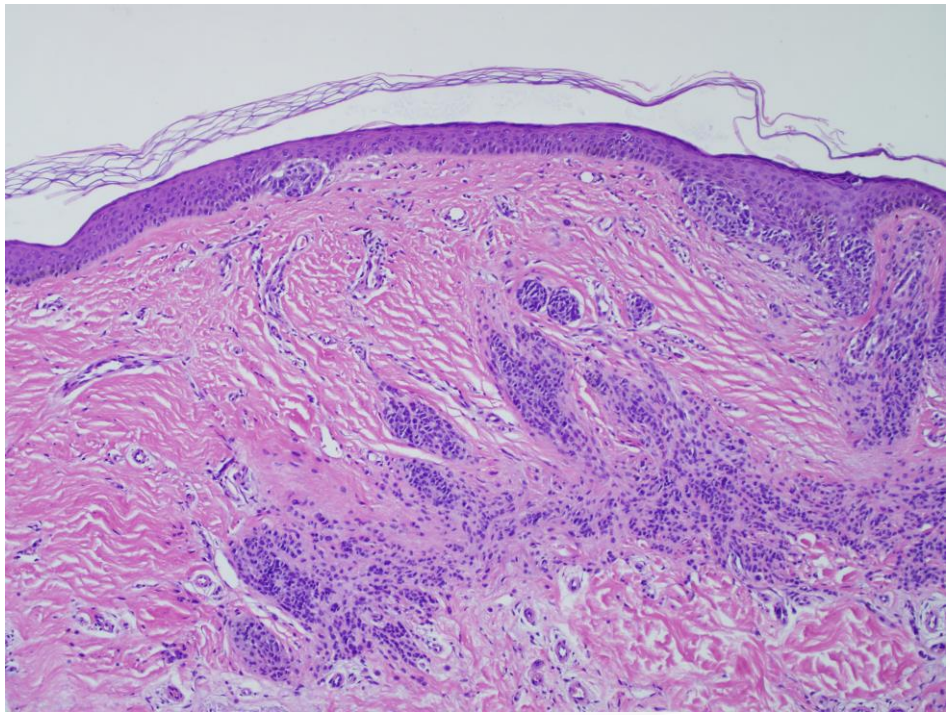
The recurrent nevus, confusing histologic features

- Recurrent nevi may demonstrate:
  - Variably-sized junctional nests of melanocytes that are often large and elongated
  - Nests may be irregularly shaped
  - Cellular discohesion
  - Enlargement of individual melanocytes
  - Pagetoid scatter often present
- Fibrosis can be confused with regression



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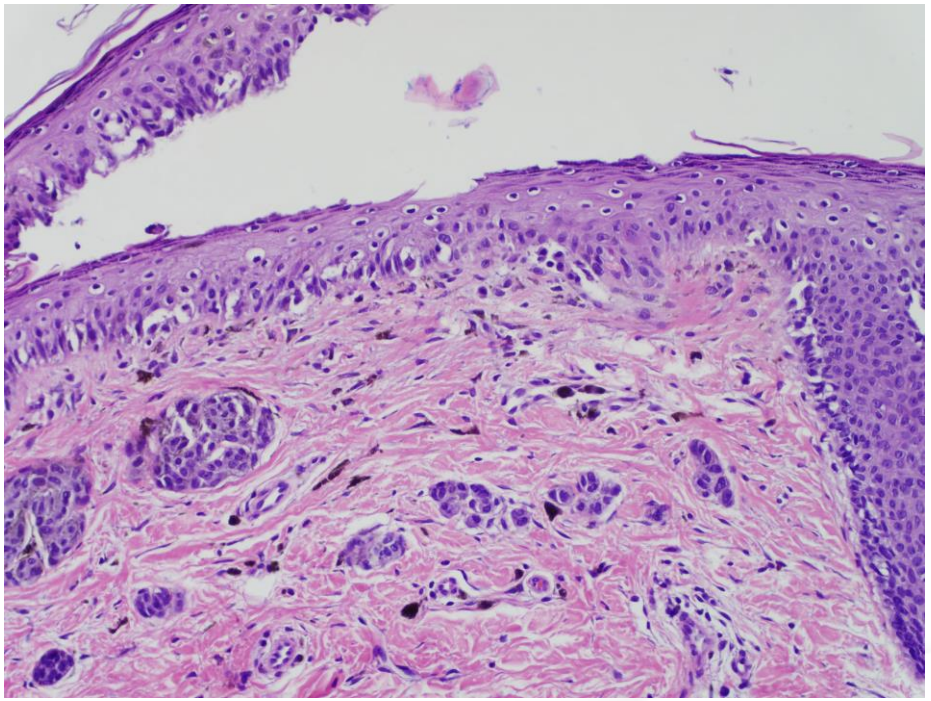

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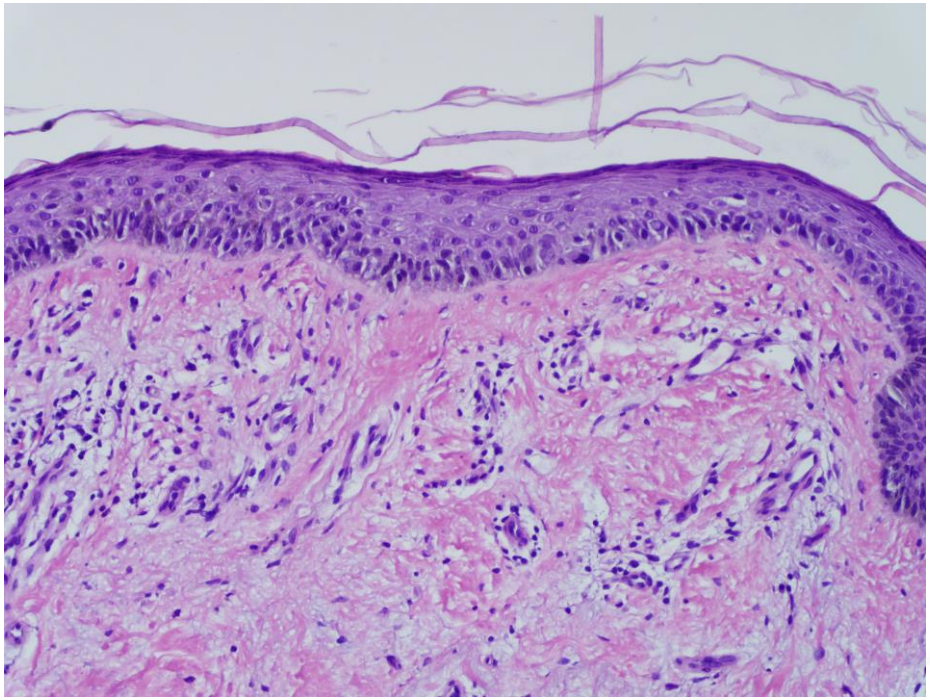
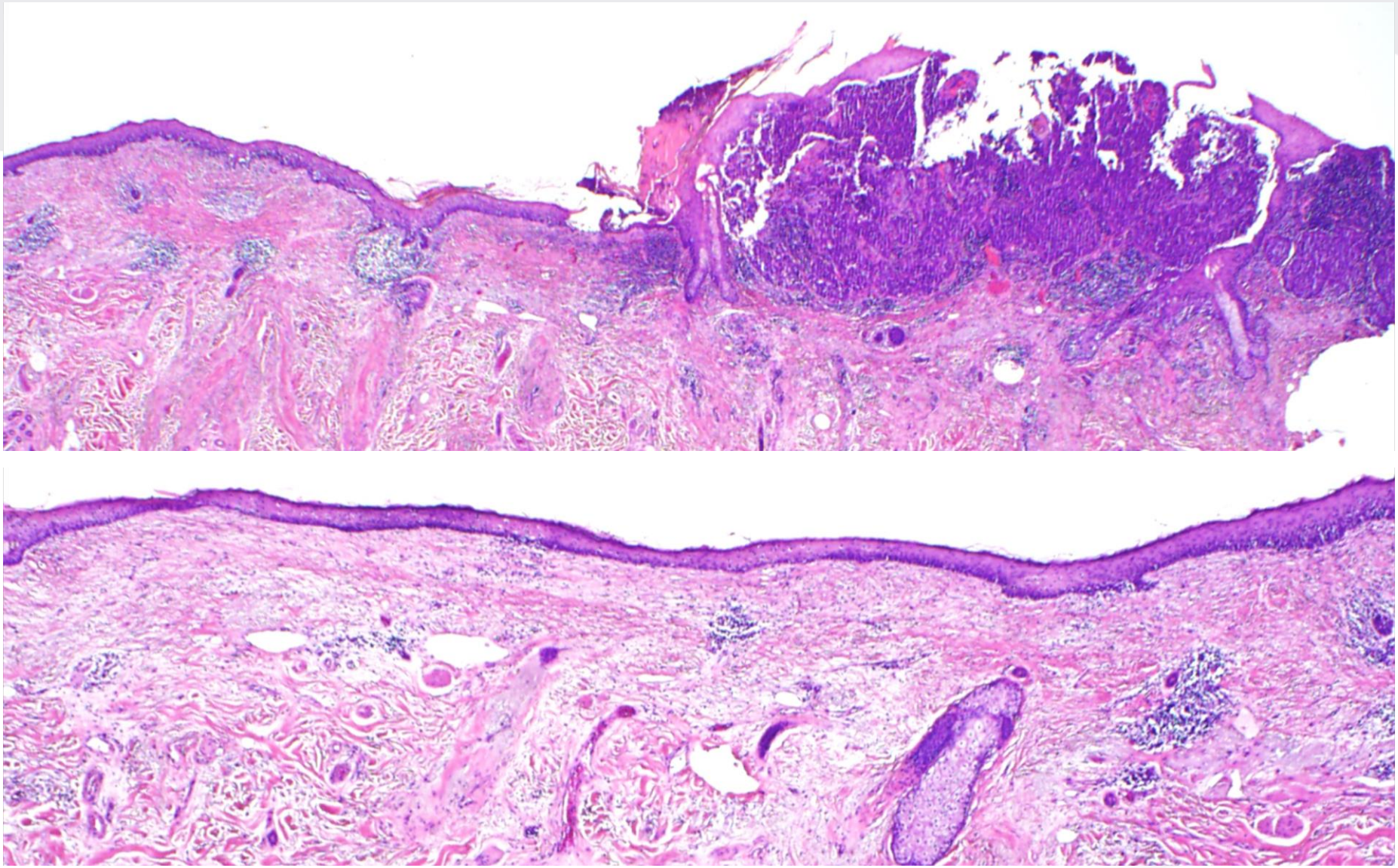
  - Pagetoid scatter often present
- Fibrosis can be confused with regression

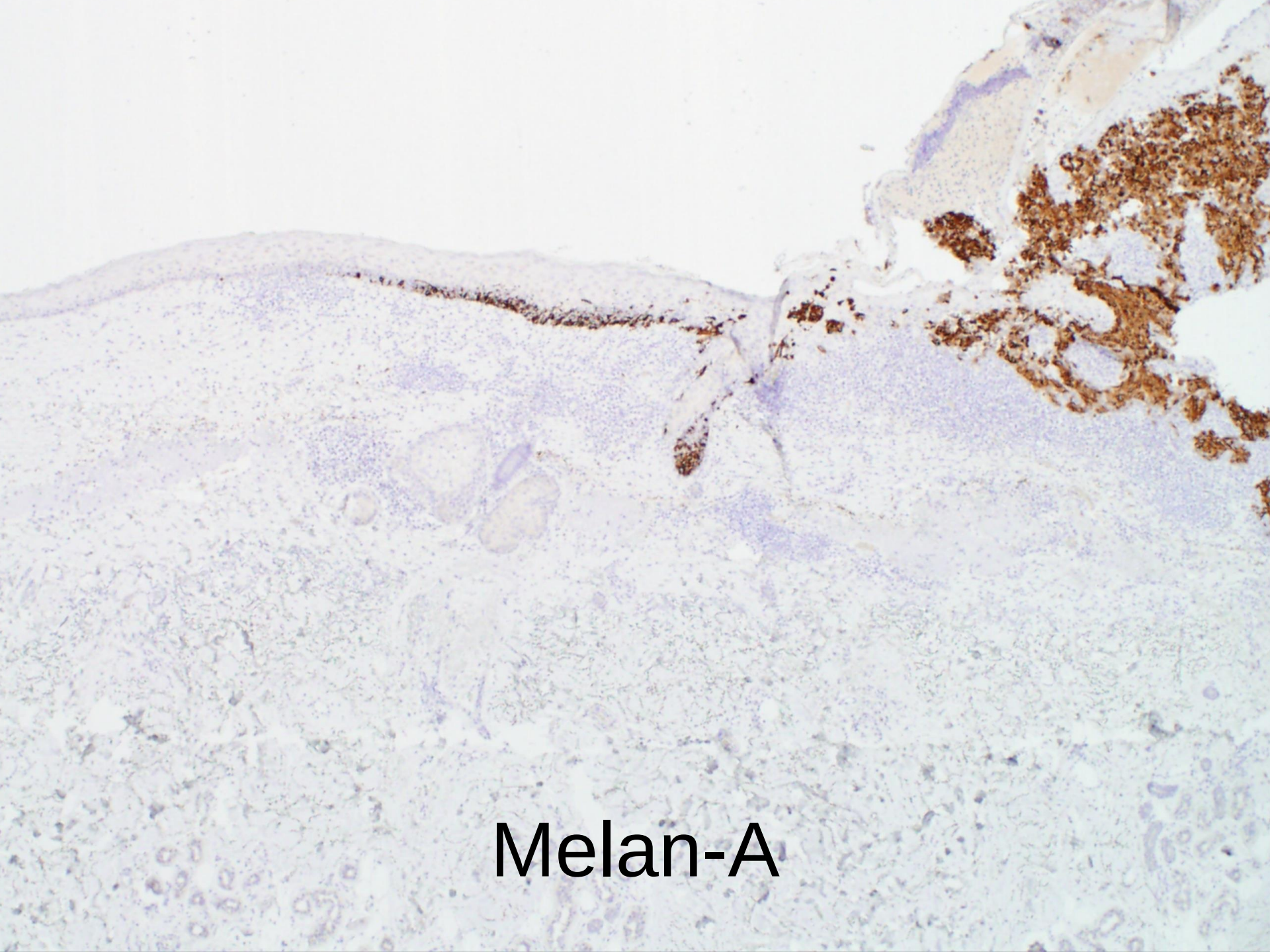


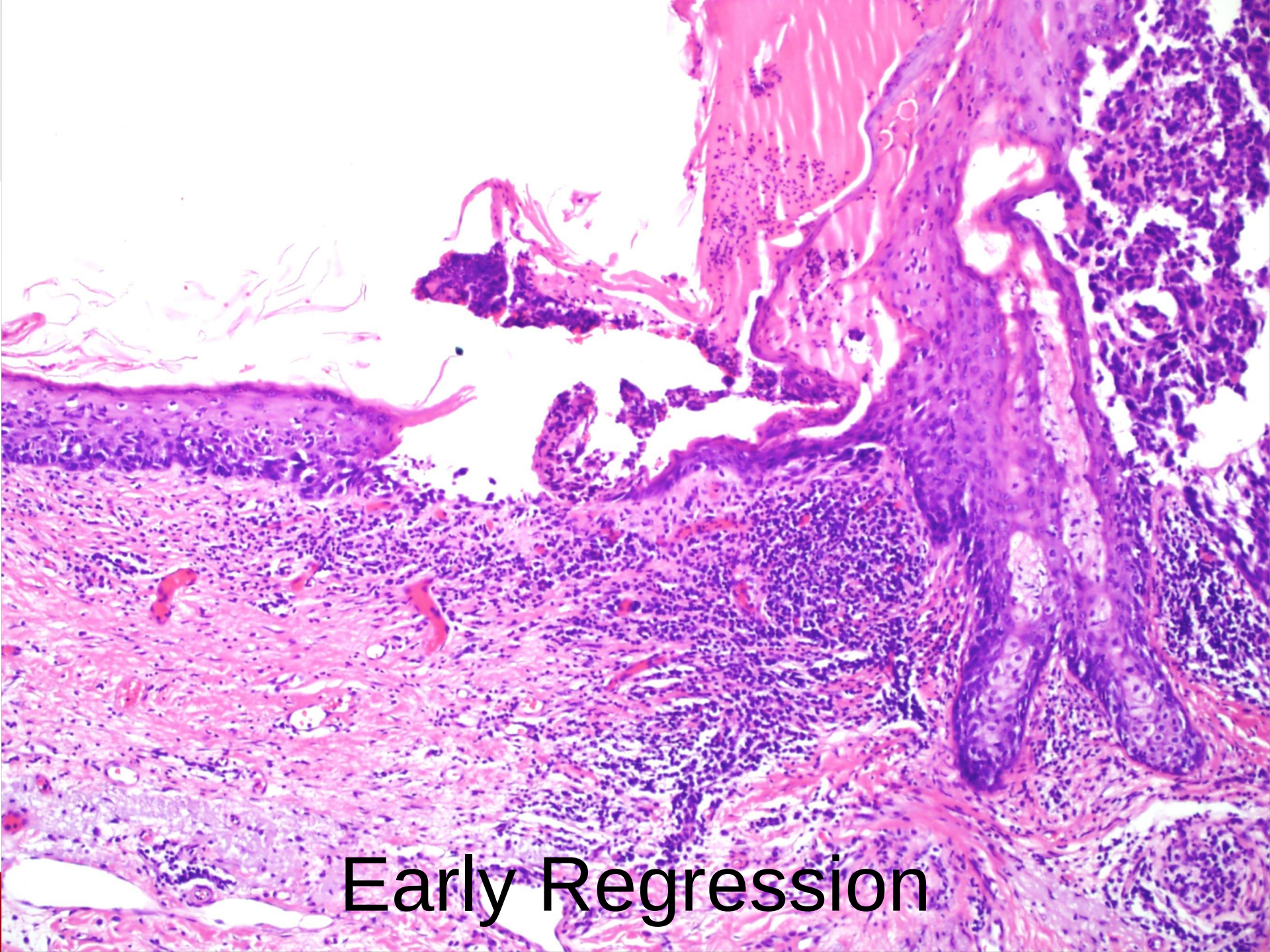
A **Practical Approach** to the **Diagnosis** of Melanocytic Lesions.
Harvey NT, Wood BA.
Arch Pathol Lab Med. **2019** Jul;143(7):789-810. doi: 10.5858/arpa.2017-0547-RA. Epub 2018 Jul 30.

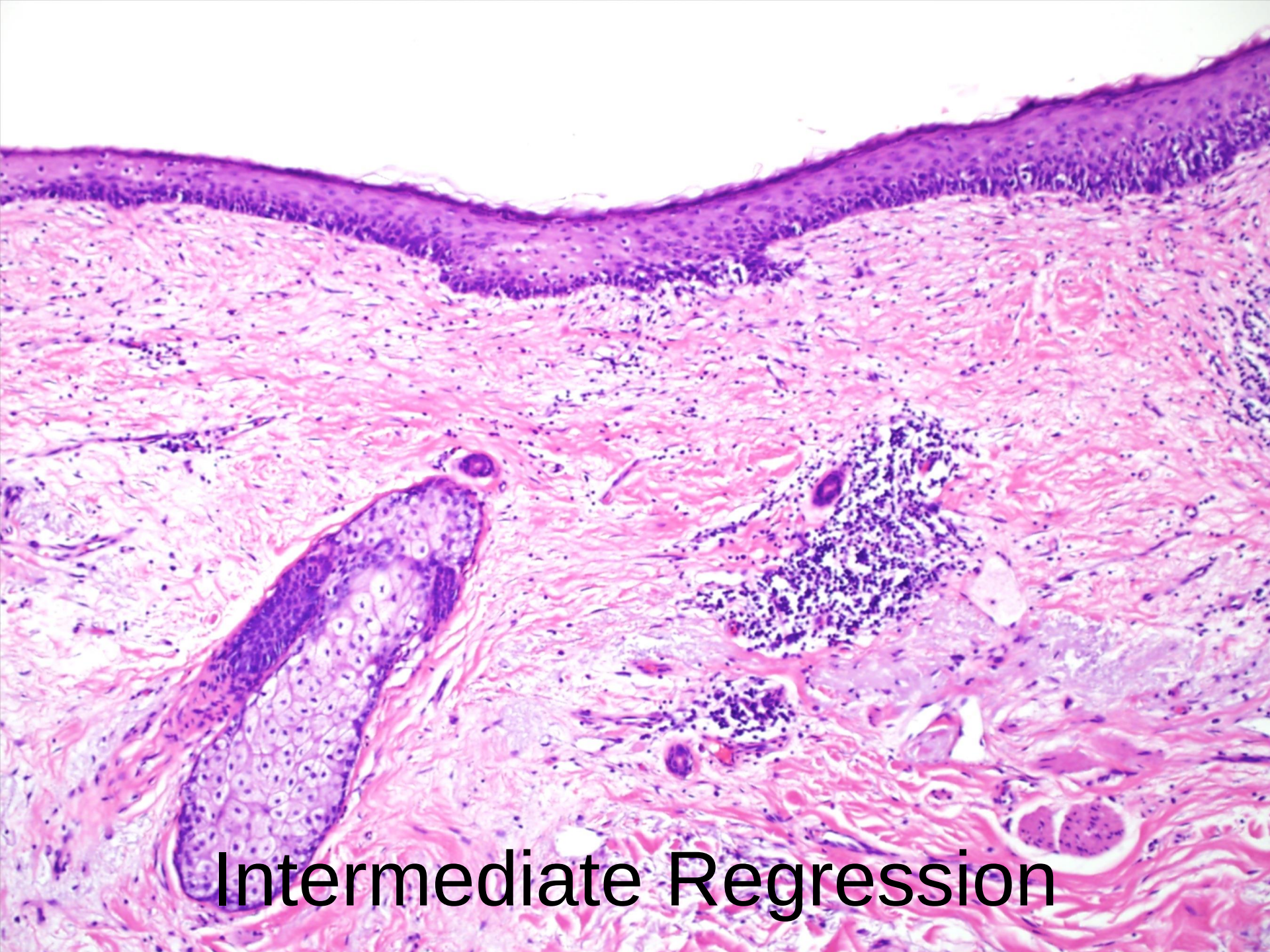
Features of regression

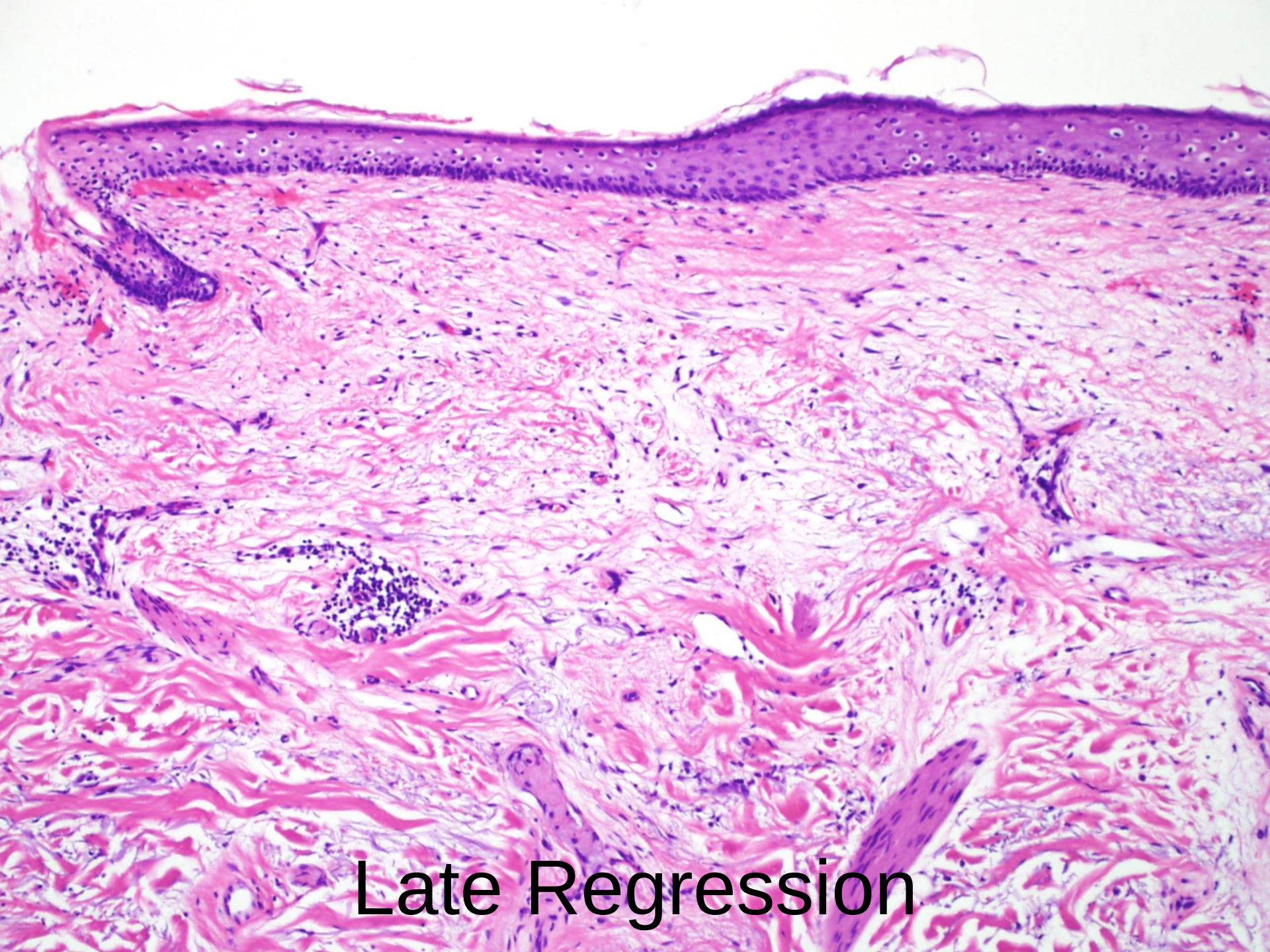
- **Early stage:**
  - Dense, band-like infiltrate of lymphocytes obscures the melanocytic proliferation
- **Intermediate stage:**
  - Junctional and dermal melanocytes decrease
  - Inflammatory response lessens
  - Residual fibrous stroma of the melanoma, with increased vascularity, becomes more evident
- **Late stage:**
  - Progression of dense fibrosis
  - Variable number of melanophages
  - Diminished to absent inflammatory infiltrate
  - Epidermal atrophy
  - Markedly decreased to absent melanocytes




Melan-A


Early Regression


Intermediate Regression


Late Regression

Regression vs Scar

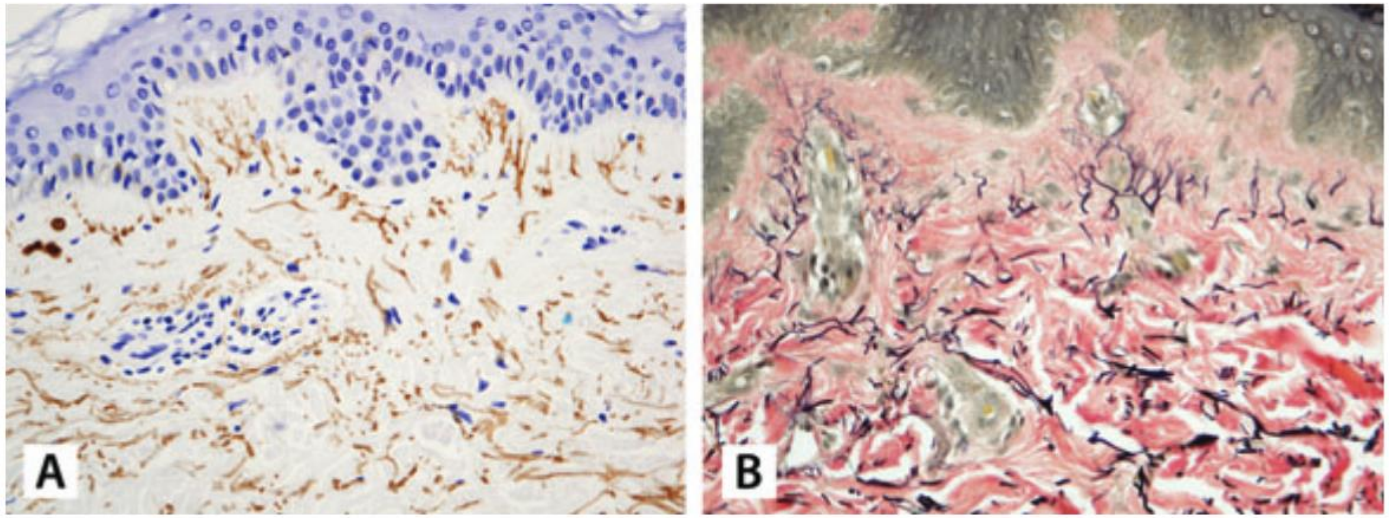
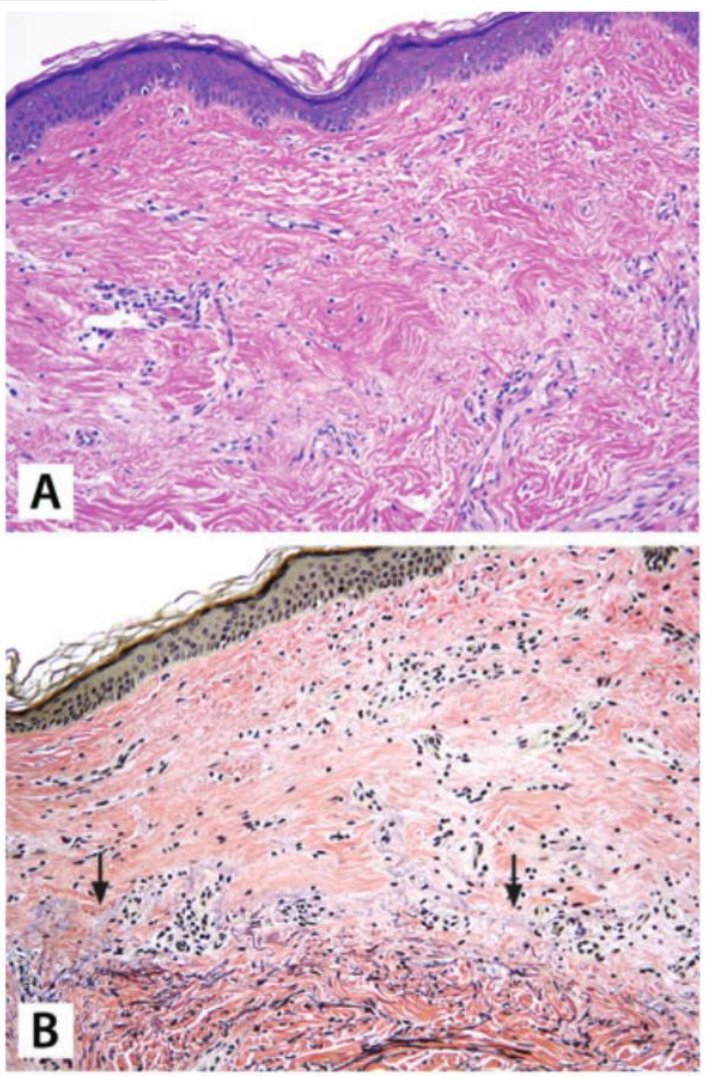


Fig. 1. Normal skin adjacent to a malignant melanoma showing the thin elastic fibers in the papillary dermis oriented perpendicularly to the epidermis in a 'candelabra' or 'fork' appearance; (A) elastin immunostain, (B) Verhoeff's elastic van Gieson stain, both ×400.

Elastic fiber pattern in regressing melanoma: a histochemical and immunohistochemical study.
Kamino H, Tam S, Roses D, Toussaint S.
J Cutan Pathol. 2010 Jul;37(7):723-9. doi: 10.1111/j.1600-0560.2010.01531.x. Epub 2010 Feb 24.

Regression vs Scar



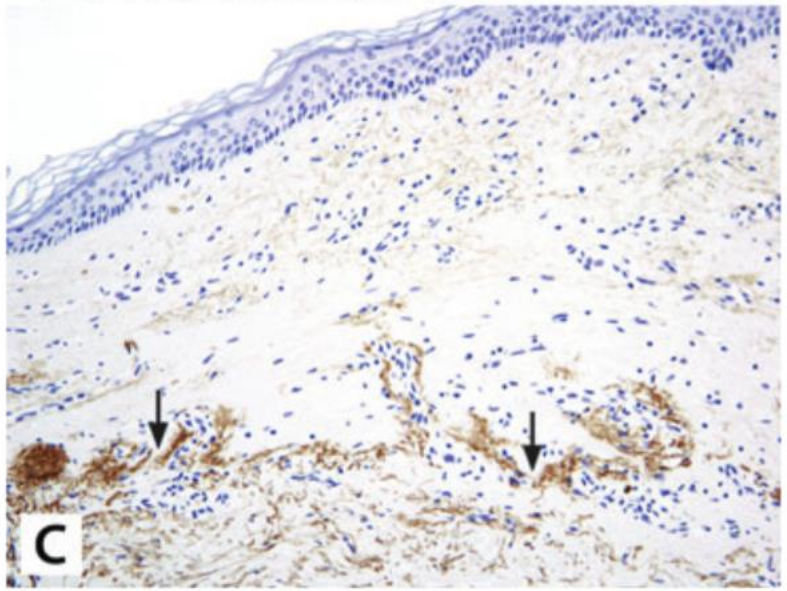


Fig. 3. Malignant melanoma with fibrosing stage of regression. There is absence of melanocytes and marked loss of elastic fibers in the area of fibrosis, but the thin elastic fibers previously found in the papillary dermis now form a compressed layer (arrows, B and C) at the base of the fibrosis. Note faint staining of regenerated thin elastic fibers in fibrosis; (A) hematoxylin-eosin stain, (B) Verhoeff's elastic van Gieson stain, (C) elastin immunostain, all ×200.

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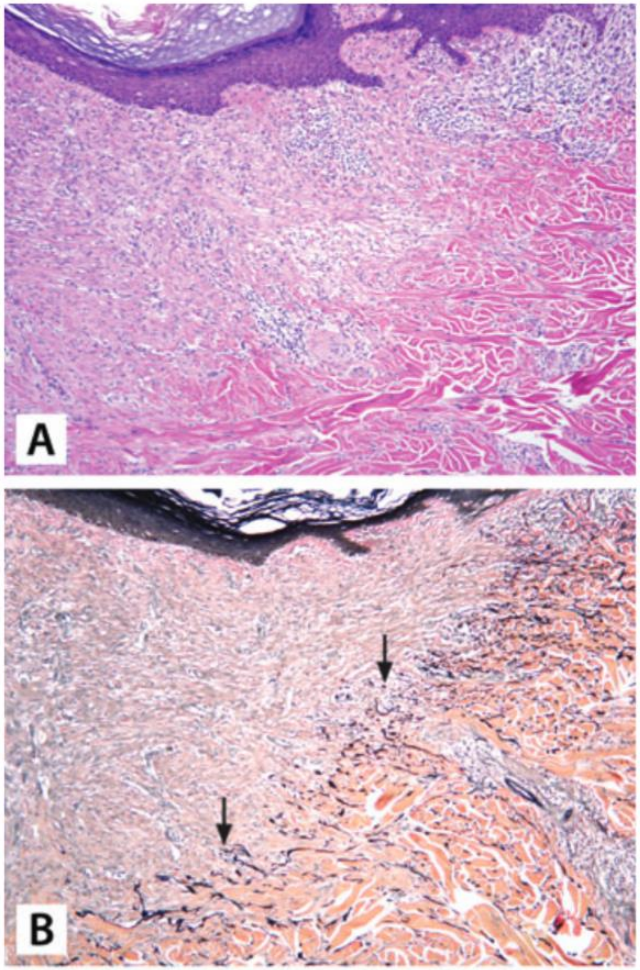

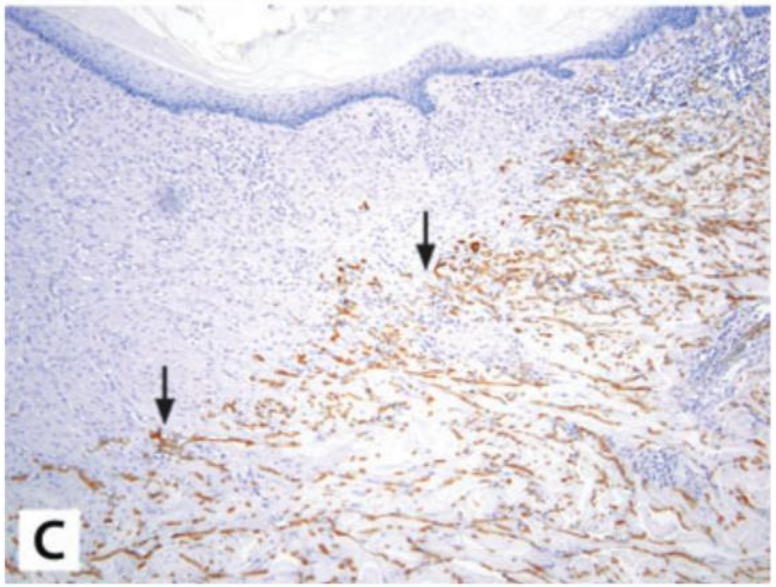

Fig. 5. Malignant melanoma associated with a scar. In contrast to regression, at the base of the scarring fibrosis, the elastic fibers are thick, coarse, wavy, fragmented and parallel to the epidermis (arrows, B and C). There is no layer of thin compressed elastic fibers at the base of the scar; (A) hematoxylin-eosin stain, (B) Verhoeff's elastic van Gieson stain, (C) elastin immunostain, all ×200.

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The recurrent nevus, other helpful hints

- Nevi tend to recur more rapidly than melanomas (weeks to months versus months to years)
- Following certain inflammatory conditions, benign nevi may resemble recurrent nevi, increasing risk for overdiagnosis
  - Stevens-Johnson syndrome
  - Lichen sclerosus – look for background changes, especially in specimens from genital skin
- Don’t hesitate to recommend complete excision if there is diagnostic uncertainty or margin involvement

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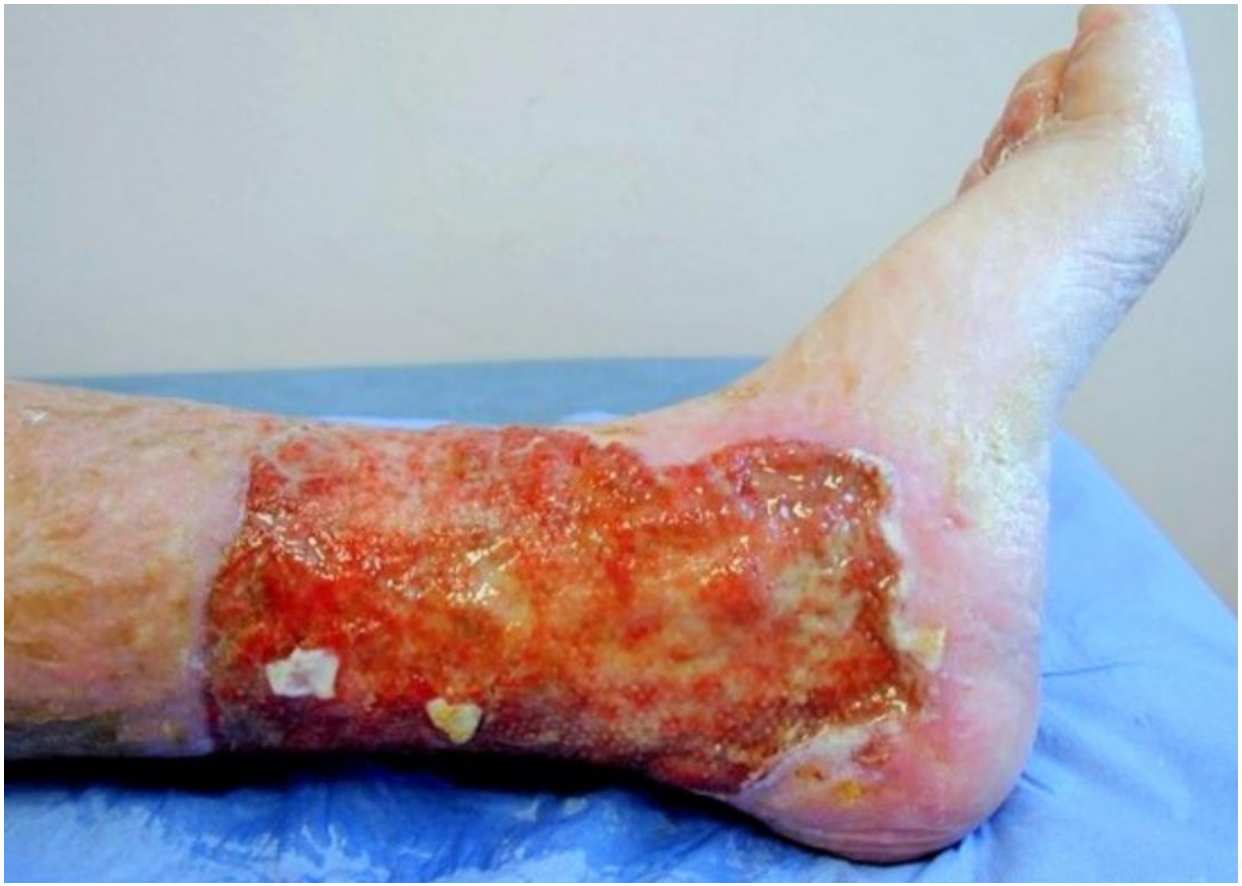
Vasculitis in biopsies from the periulcer edge



Histopathologic vasculitis from the periulcer edge: A retrospective cohort study

Cristian D. Gonzalez, MD,[a] Scott R. Florell, MD,[a] Anneli R. Bowen, MD,[a]
Angela P. Presson, PhD,[b] and Marta J. Petersen, MD[a]
Salt Lake City, Utah

J Am Acad Dermatol
December 2019

- 62 specimens from 56 patients were examined
- Vasculitis was present in 32 of the periulcer specimens (51.6%)
- Diffuse vasculitis (involvement of 3 or more vessels) was seen in 9 specimens
- Focal vasculitis was seen in 23 specimens
- Only 3 patients were found to have ulcers secondary to systemic vasculitis
- Among the patients with diffuse vasculitis on histology, the probability of having true vasculitis was 33.3%

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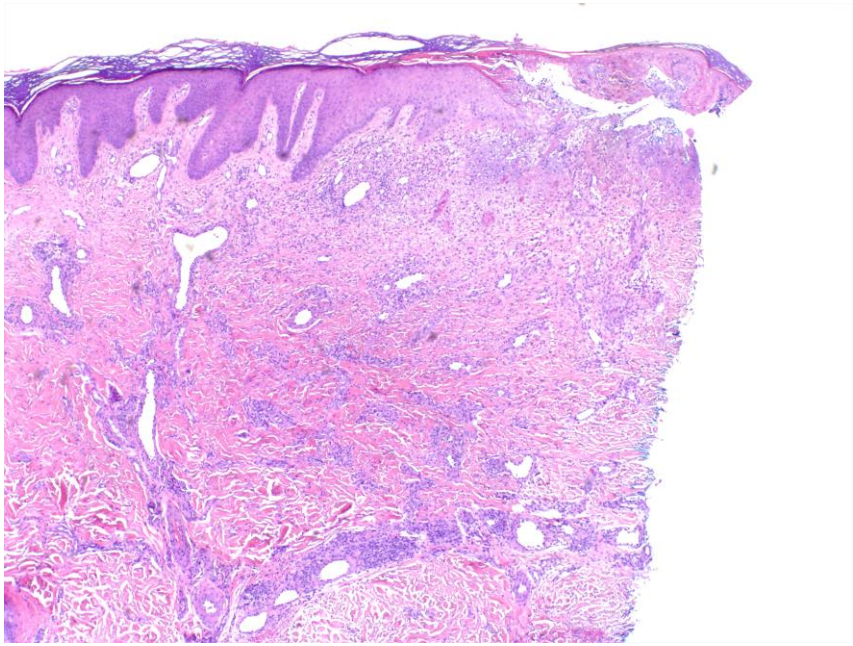
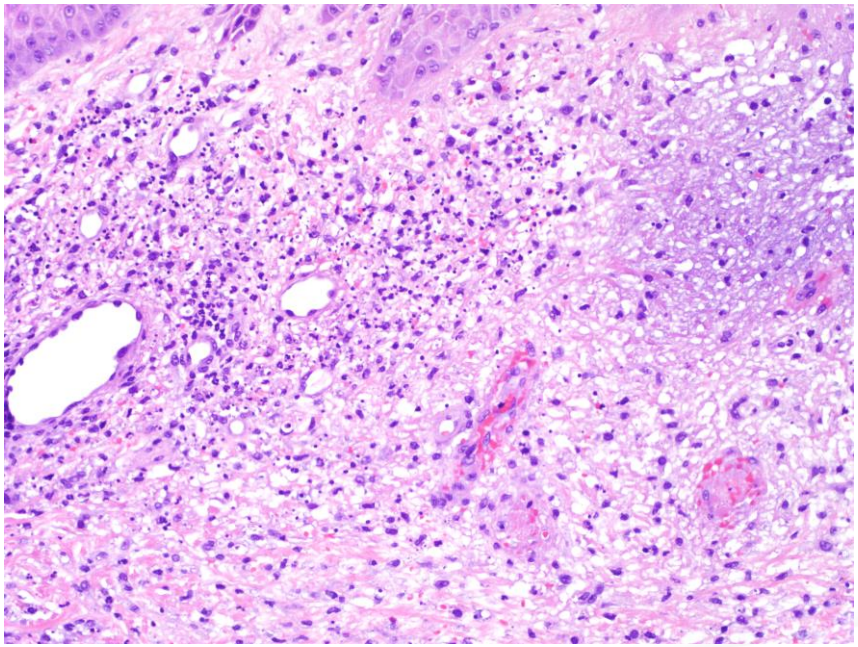
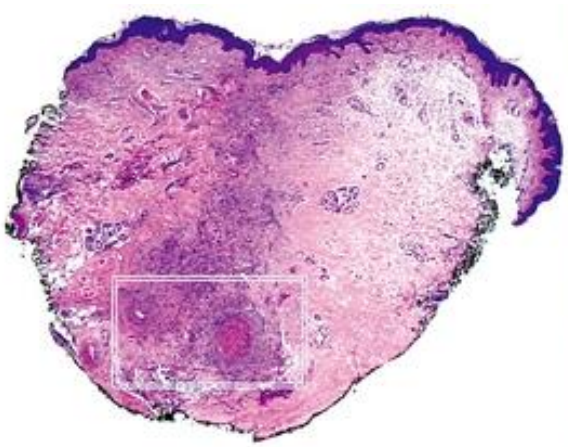
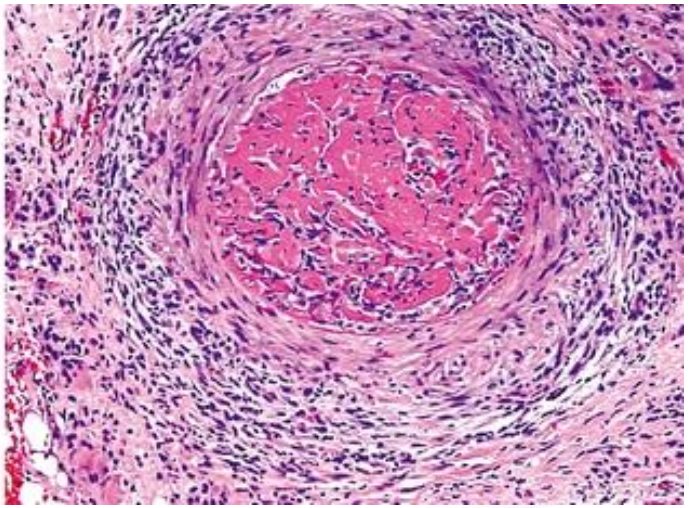




Other Causes of Incidental Vasculitis

- Neutrophilic dermatoses
  - Vasculitis may be seen incidentally in areas with dense neutrophilic infiltrates in contrast to the angiocentric neutrophilic infiltrate of authentic LCV
- Re-excision specimens



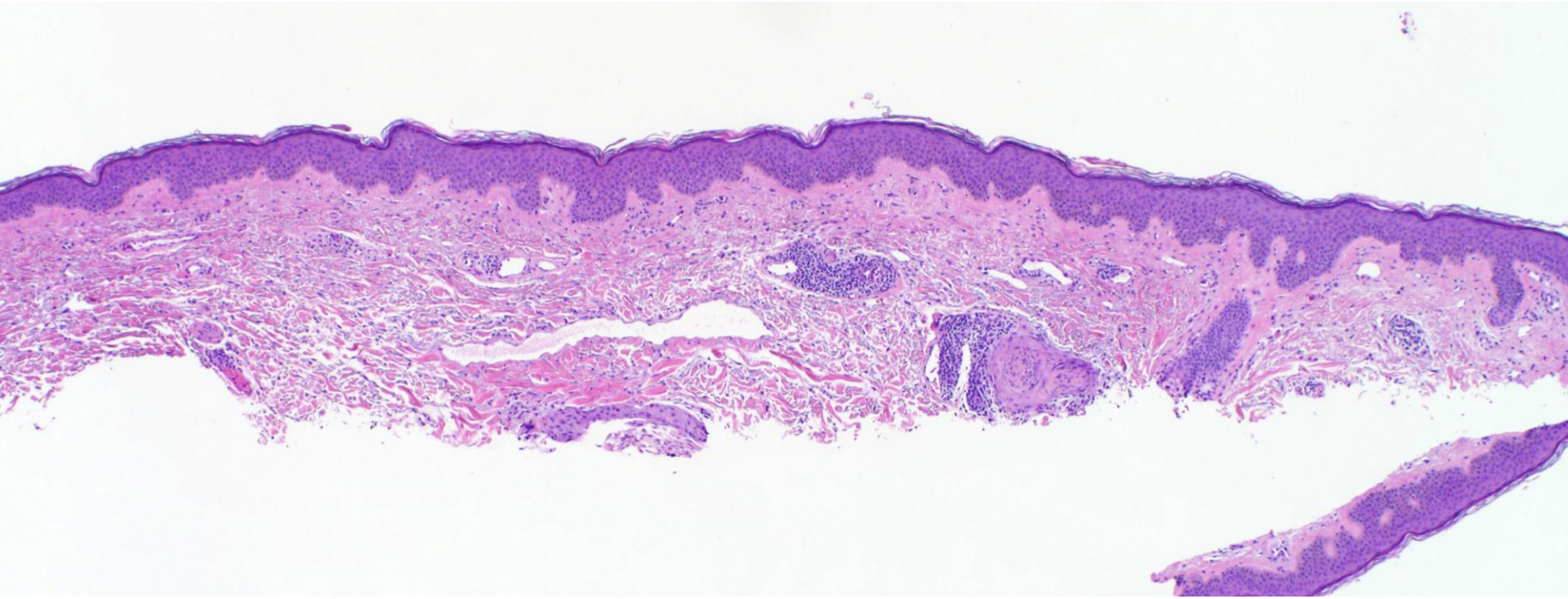


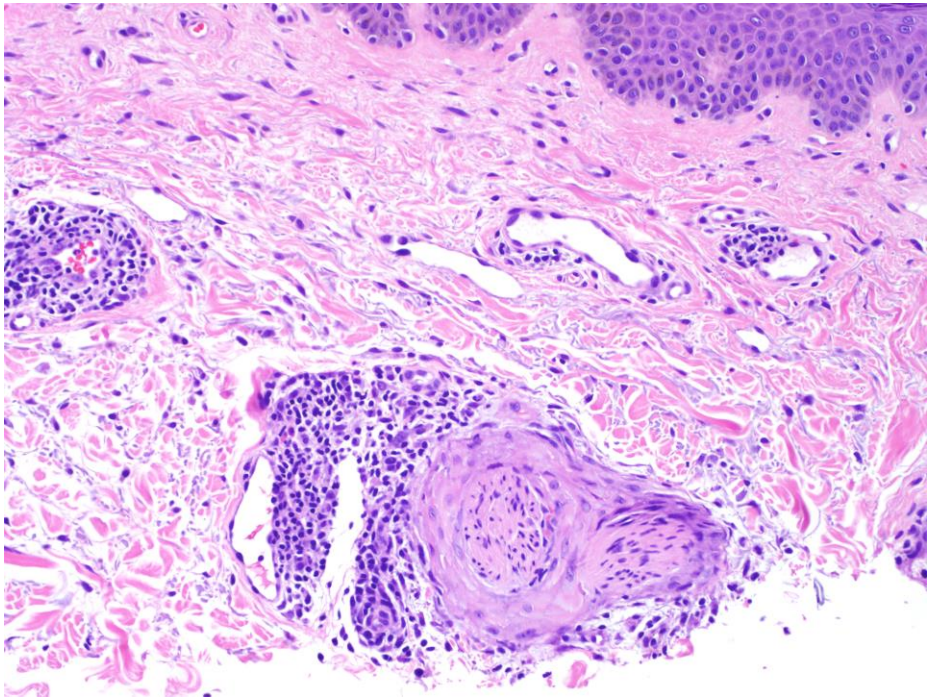
Histopathology, Volume: 56, Issue: 1, Pages: 3-23, First published: 23 December 2009, DOI: (10.1111/j.1365-2559.2009.03443.x)

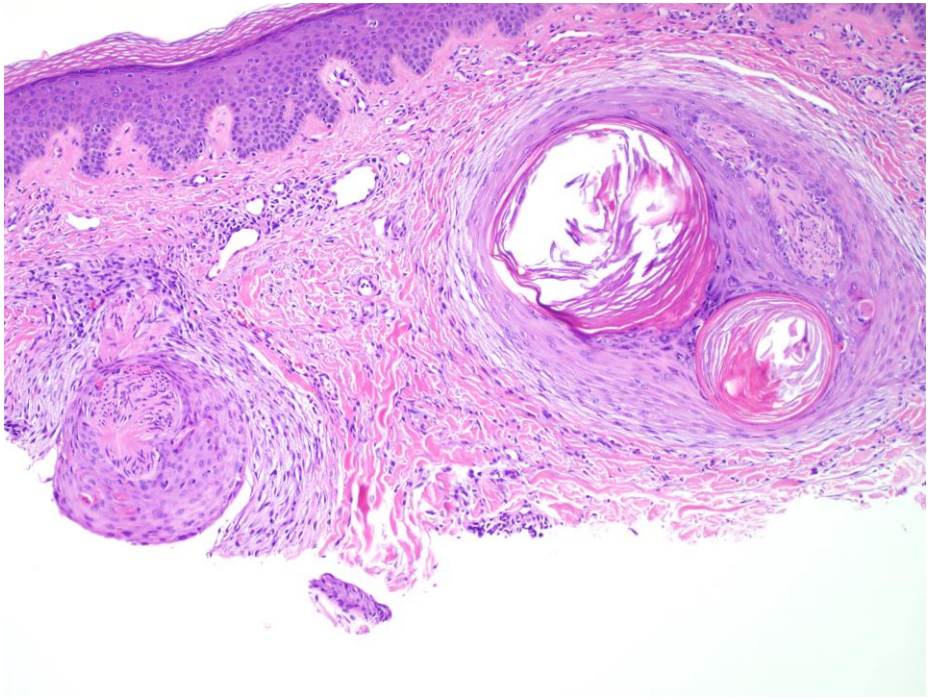
Issues raised

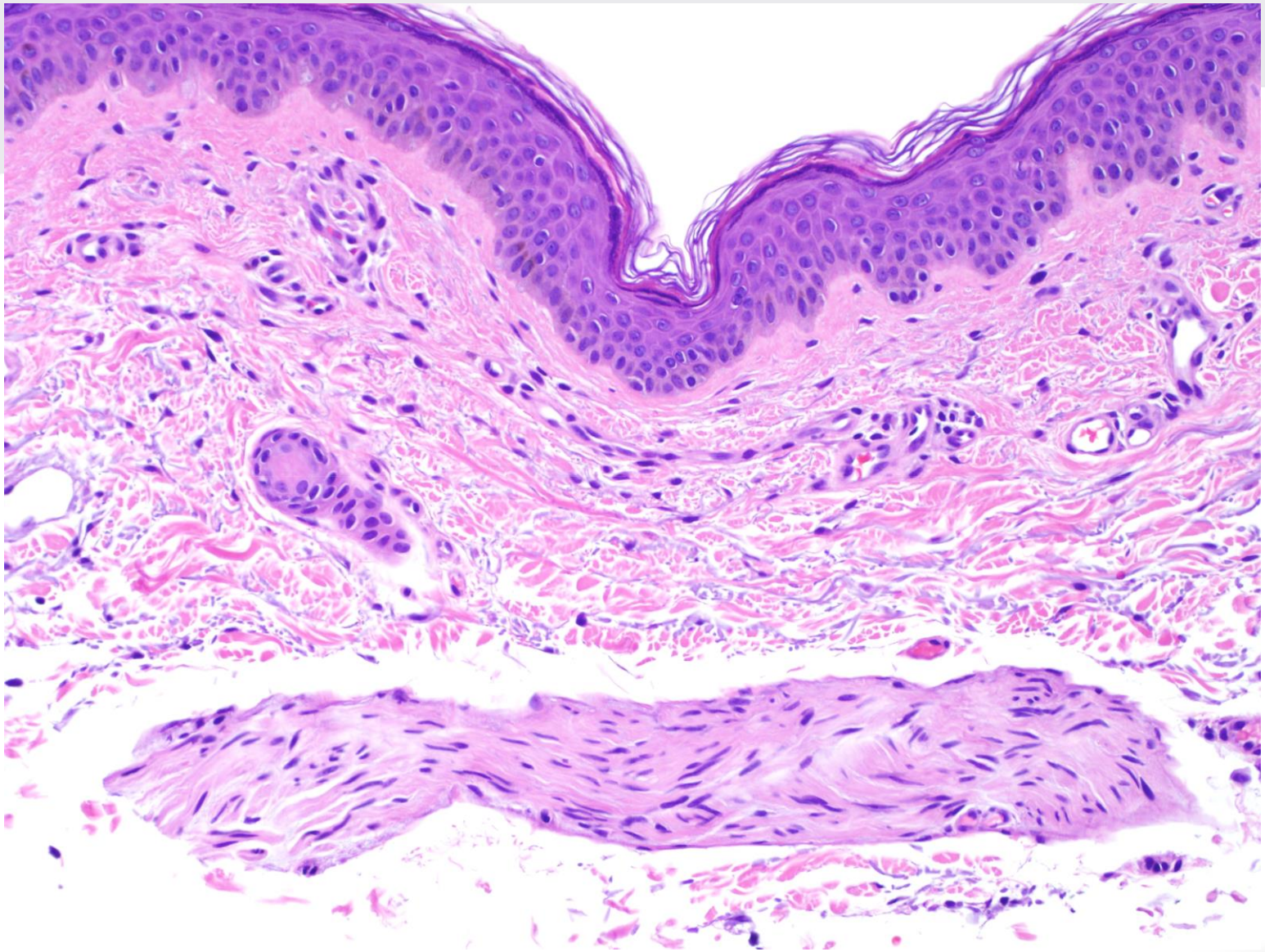
- Incidental vasculitis should be considered in the appropriate clinical scenarios
- If vasculitis is overemphasized:
  - True etiology of disease processes may not be appreciated (such as pyoderma gangrenosum or vasculopathy)
  - Patient may receive unnecessary systemic therapy for vasculitis
  - Unnecessary diagnostic testing may lead to additional medical costs and/or non-specific incidental findings.

An uncommon diagnosis may simulate perineural invasion



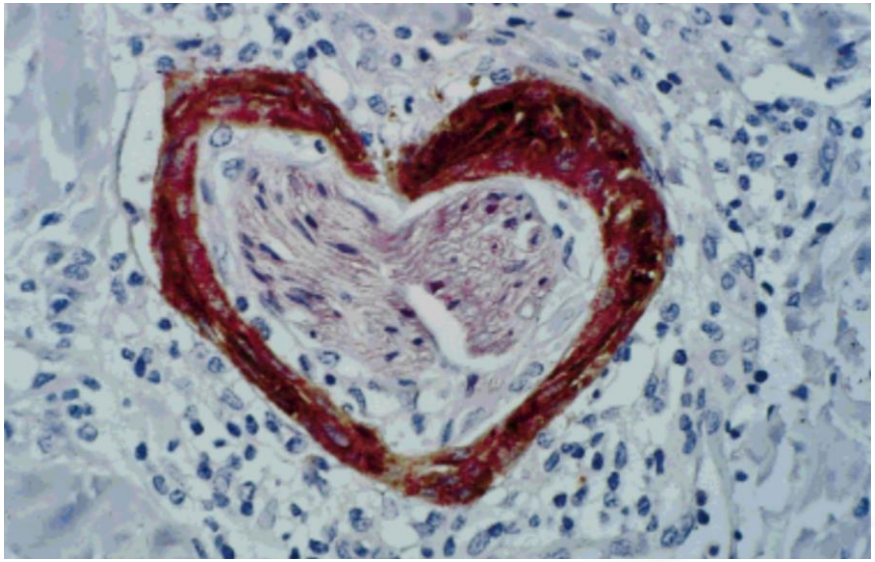






Epithelial Sheath Neuroma

- Rare benign process of unknown pathogenesis, first reported in 2000
- Typically presents as a solitary flesh-colored papule on the upper back of adults
- Sometimes itchy
- Debate as to whether this entity is a neoplasm or reactive process.



Heinz Kutzner (2001). For Valentine's Day: Epithelial Sheath Neuroma Cancer, 91 (4)

Epithelial Sheath Neuroma

- Characterized histologically by multiple enlarged peripheral nerve fibers ensheathed by mature squamous epithelium
  - Epithelium surrounding nerves can raise concern for carcinomatous perineural invasion
- Generally limited to the superficial dermis
  - One case has shown a connection to the epidermis and another has purported extension into the subcutis.
- Often surrounded by a loose myxoid stroma, lymphocytic infiltrate, and sometimes prominent infundibular cysts
- Should be no history of prior biopsy in the area to make diagnosis
  - Similar findings may be found in areas of prior procedure/surgery

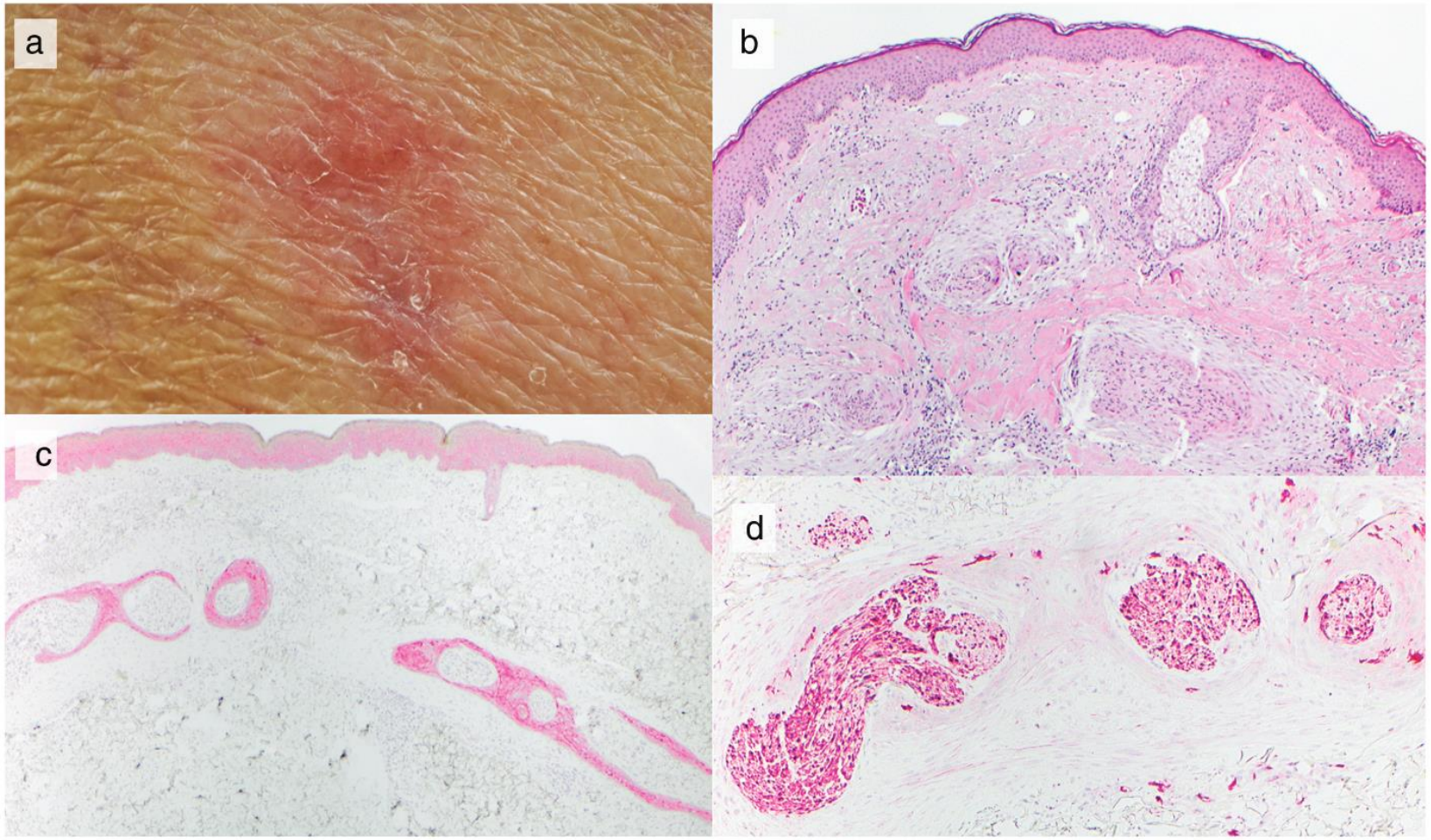
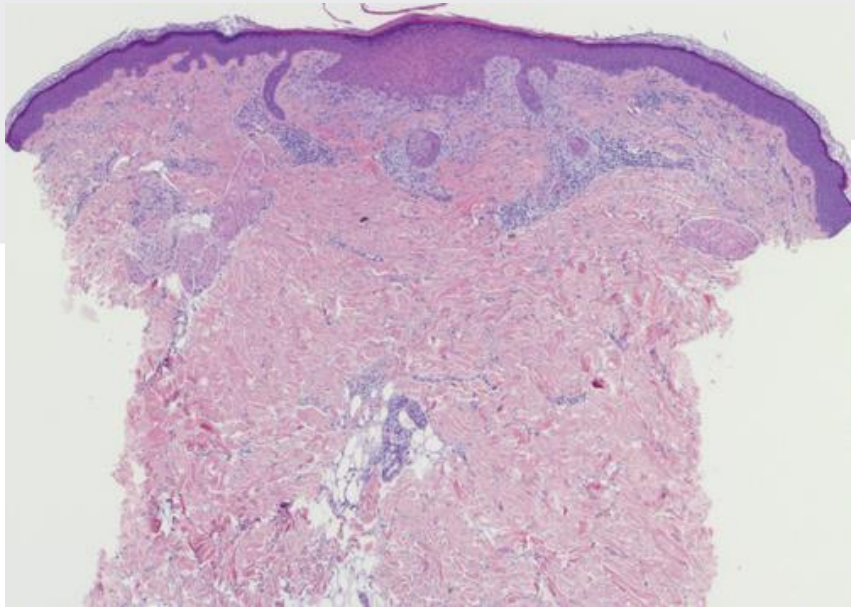


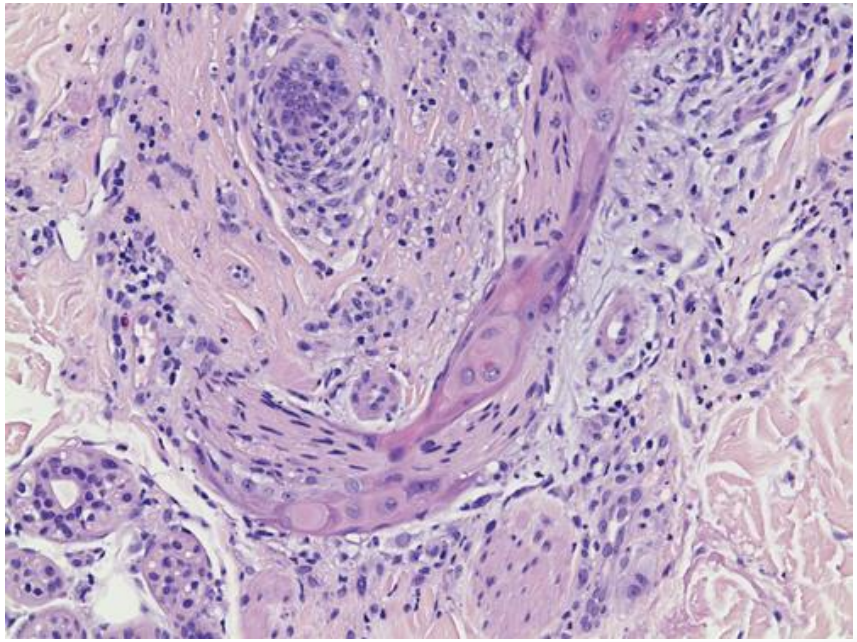
Figure 1 Clinical and histological findings of the biopsy. Erythematous plaque (1.5 × 2 cm) on the upper back (a). Increased and slightly enlarged nerve fiber bundles in the upper dermis coated by a pan-cytokeratin-positive epithelial sheath without cellular atypia (b–d). Hematoxylin-eosin stain [HE] (original magnification x 100) (b). Pan-cytokeratin [pan-CK] stain of the epithelial sheath (original magnification x 100) (c). S100 stain of the nerve fibers (original magnification x 200) (d).

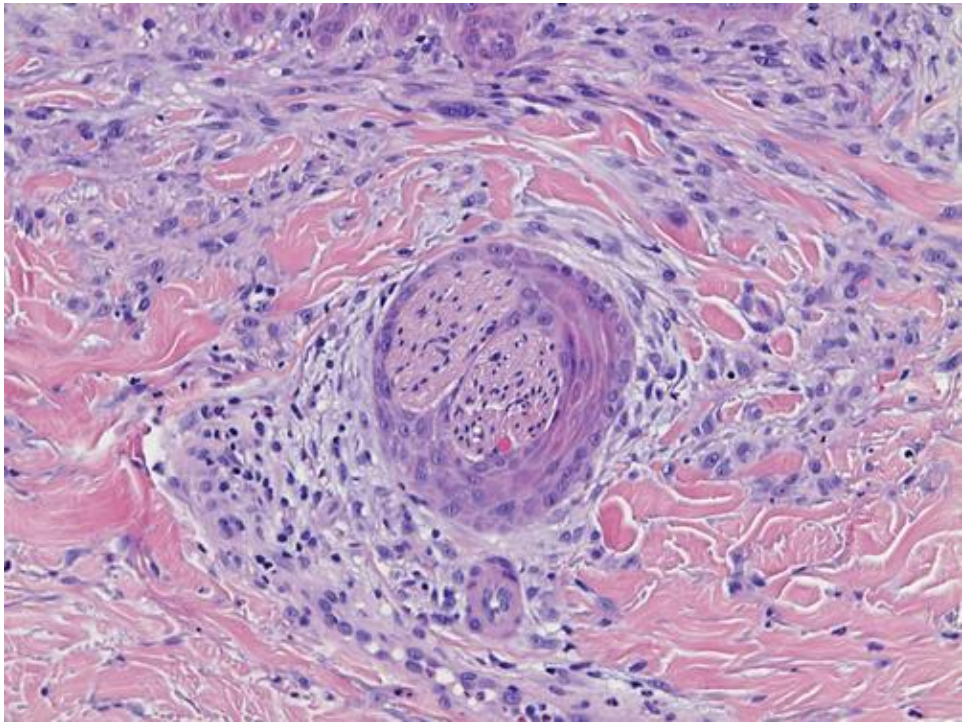
J Dtsch Dermatol Ges. 2018 Jul;16(7):940-944. doi: 10.1111/ddg.13558. Epub 2018 Jun 21.

An unusual erythematous plaque on the back of an elderly woman.

Franz R[1], Hein R[1], Biedermann T[1], Christian A[1,2].







J Cutan Pathol. 2016 Jun;43(6):531-534. doi: 10.1111/cup.12693. Epub 2016 Apr 1.

Epithelial sheath neuroma: evidence supporting a hyperplastic etiology and epidermal origin.

Hirano-Ali SA[1], Bryant EA[2], Warren SJ[3].

Epithelial Sheath Neuroma – Take Home Points

- Beware if there is concurrent squamous cell carcinoma or scar
- Epithelium should not be atypical
- Enlarged superficial nerves may serve as a clue to diagnosis
- Epithelium surrounding a nerve does not equal perineural invasion!!!


Questions?

Additional References

- Weedon's Skin Pathology, 4th edition, James W Patterson, 2016. Pages: 822-823.
- Llor C. Reducing overdiagnosis in primary care is needed. Eur J Gen Pract. 2017; 23:215-216.
- Chen KT. Reactive neuroepithelial aggregates of the skin. Int J Surg Pathol. 2003 11(3):205-10.