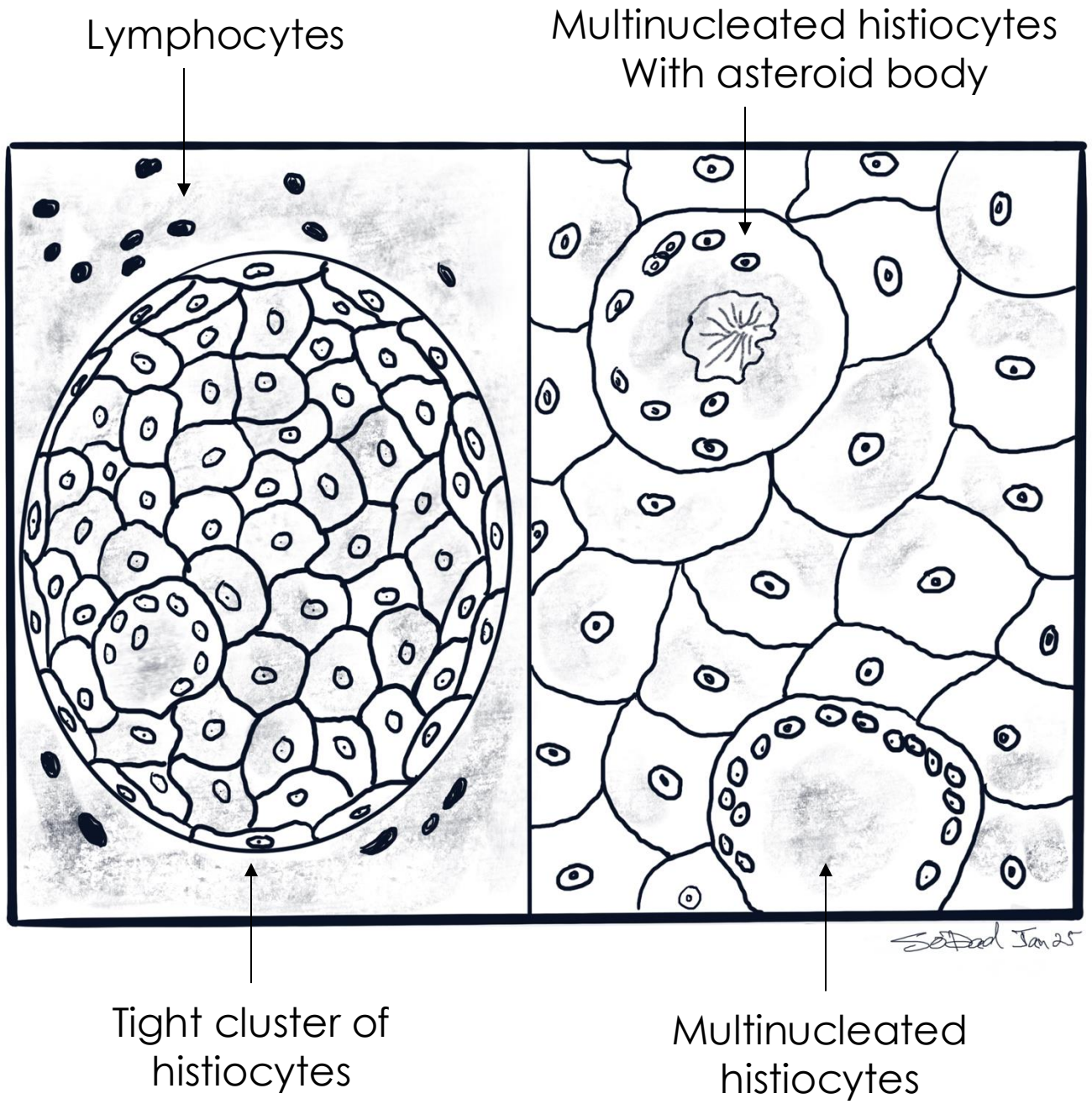
Granulomatous, necrobiotic and perforating dermatoses

Soheil S. Dadras MD-PhD

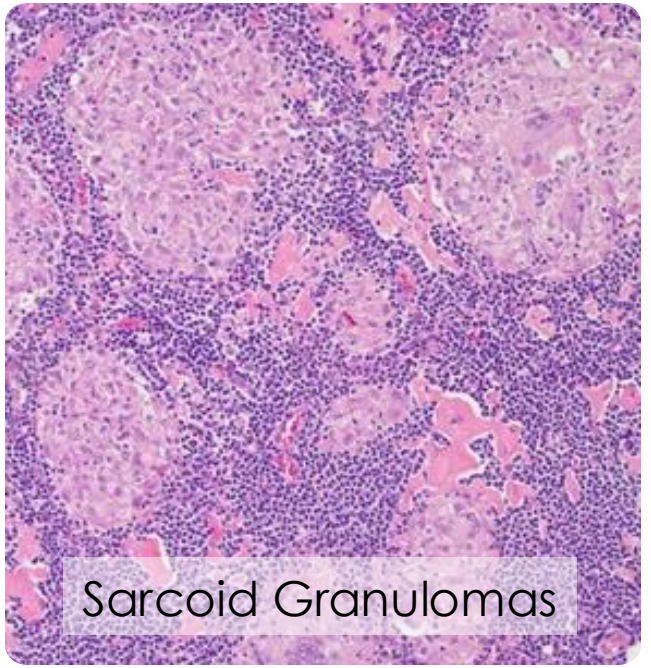


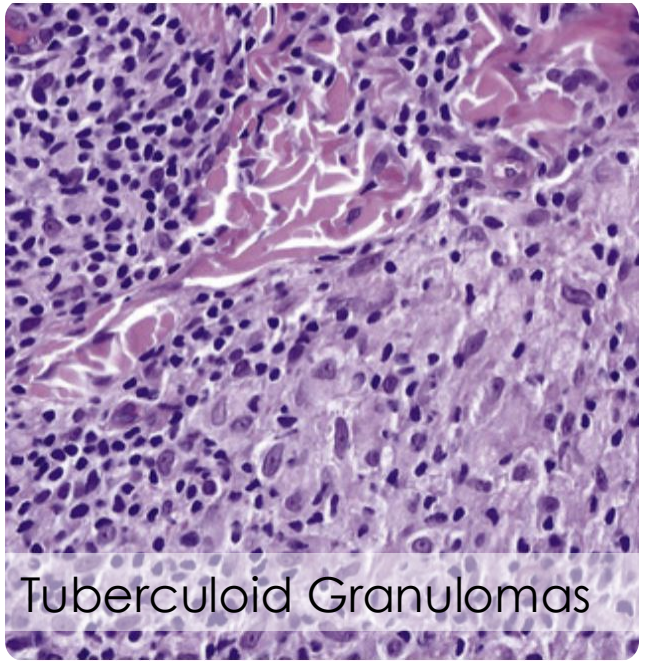
What is a granuloma?

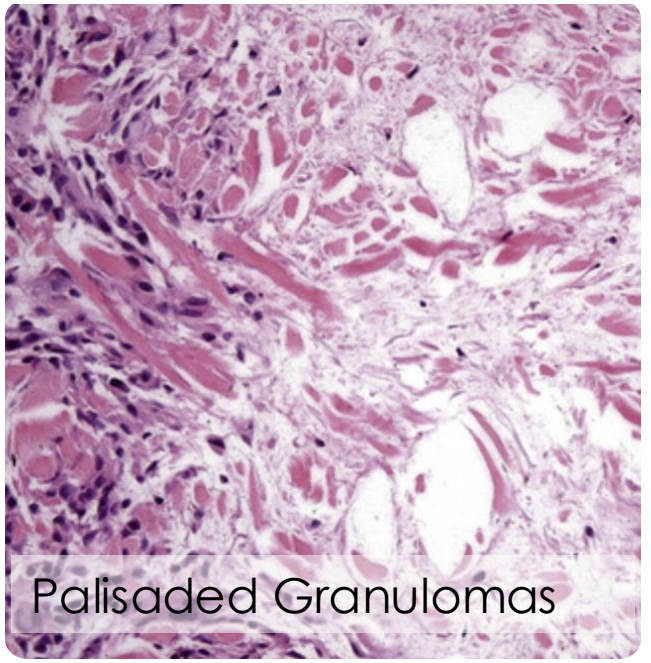
- **Granuloma:** Aggregations of tissue monocytes or macrophages (histiocytes) ± inflammatory cells
  - Early Disease: Aggregations of histiocytes not well-defined.

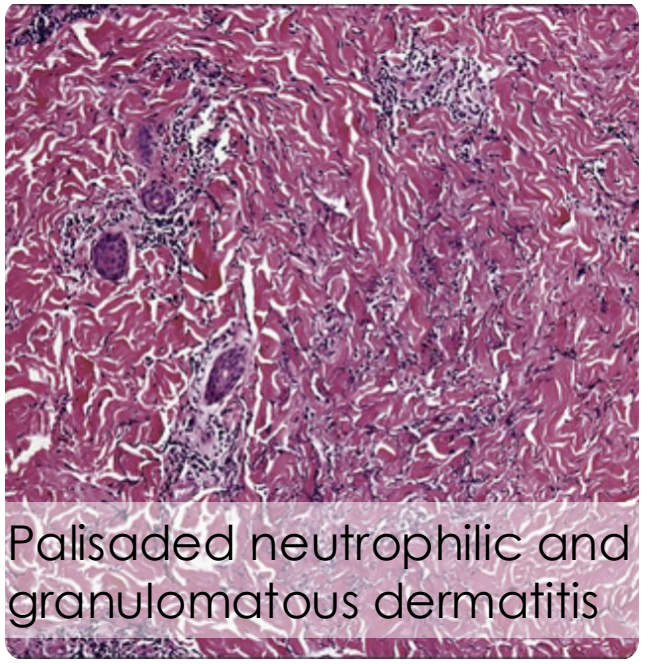
Sarcoidal granuloma

What is the histopathology of granuloma subtypes?


Sarcoid Granulomas


Tuberculoid Granulomas


Palisaded Granulomas


Palisaded neutrophilic and granulomatous dermatitis

What are granuloma subtypes?

- **Types of Granulomas**
  1. Naked/Sarcoidal Granulomas: Few surrounding lymphocytes.
  2. Tuberculoid Granulomas: Rimmed by lymphocytes.
  3. Palisaded Granulomas: Histiocytes form around central degeneration/necrosis.
  4. Palisaded neutrophilic and granulomatous dermatitis: necrobiosis, ill-formed histiocytes, and neutrophils.

What are some granuloma mimics?

- **Exclusion Criteria**:
  - Infectious agents (via special stains: Fite, AFB, GMS, PAS, and Gram)
    - Molecular assay: targeted PCR followed by 18S rRNA sequencing
  - Foreign materials (via polarization microscopy, scoring lines)
  - NK/T-cell lymphoma (lethal midline granuloma; via IHC lymphoma workup)
  - Epithelioid sarcoma (IHC: EMA, pan-keratin)
- **IHC:** CD68, CD163, Lysozyme

Granulomatous infiltrate/dermatitis

Sarcoidosis

Clinical Features:

- Systemic disease affecting lungs, eyes, lymph nodes, skin
- "Lupus pernio": violaceous nodules on nose, cheeks, earlobes
- Brown-purple papules, nodules, plaques, scarring alopecia, lesions on scars/tattoos

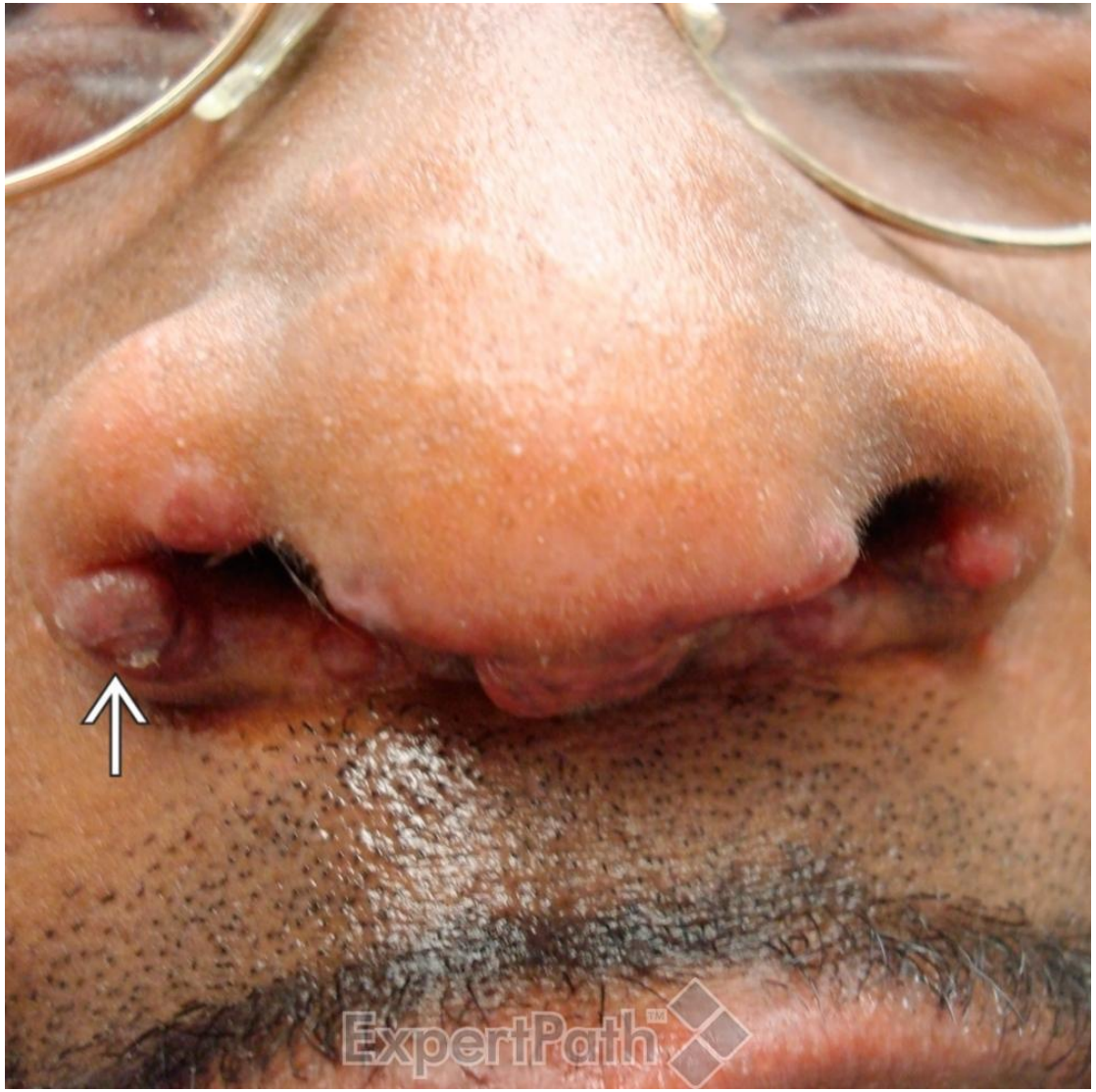
Histopathologic Features:

- Naked epithelioid granulomas, lacking well-developed lymphocyte cuff
- Asteroid bodies, Schaumann bodies, Hamazaki-Wasserman bodies (calcium oxylate crystals)

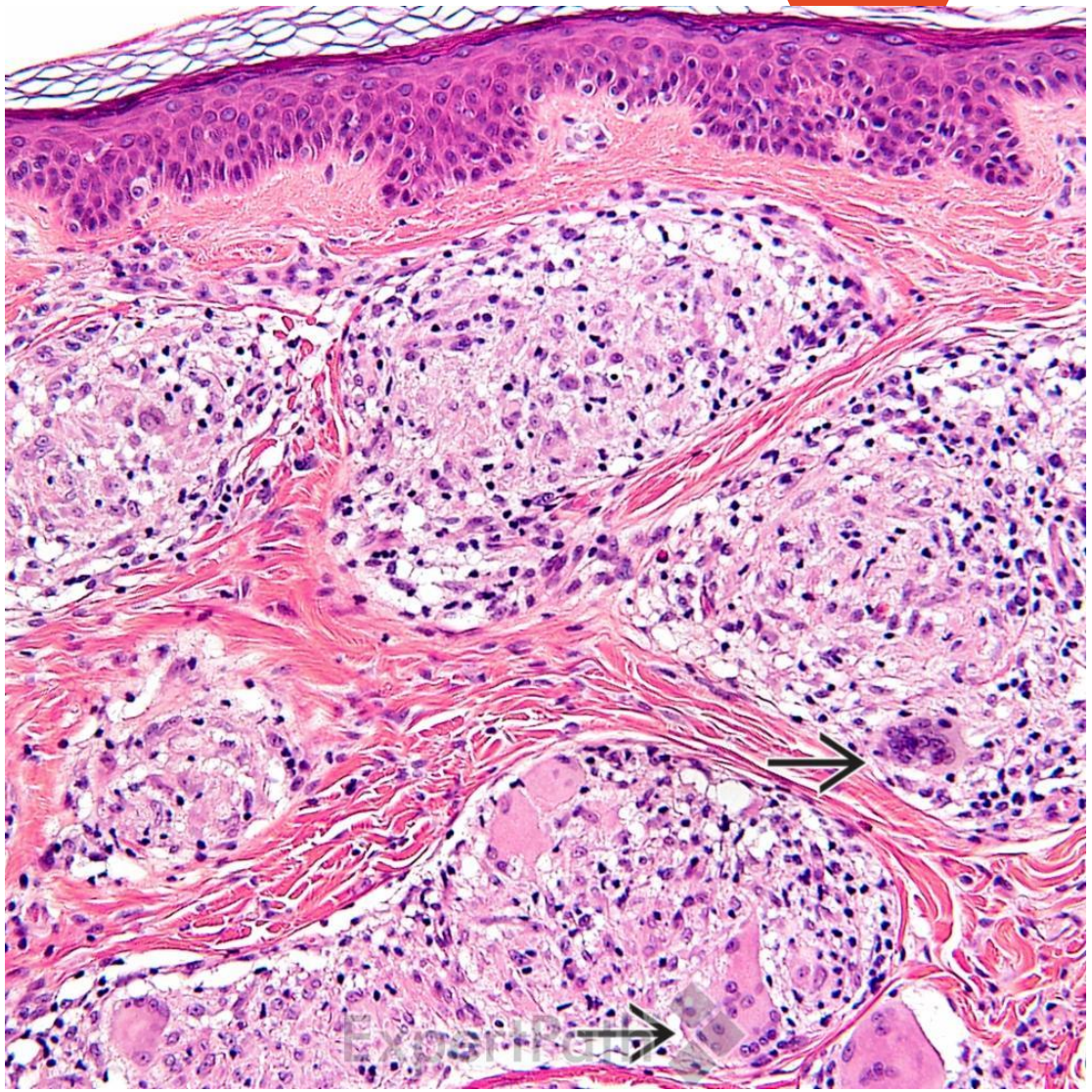
Differential Diagnosis:

- Orofacial granulomatosis (e.g., acne rosacea, perioral dermatitis)
- Infectious agents (e.g., tuberculosis, leprosy)
- Foreign body granulomas
- Lymphoproliferative disorders (granulomatous slack skin, i.e. CTCL

Sarcoidosis



Sarcoidosis presents as apple jelly-colored, slightly pink, discrete papules (white solid arrow) on the nose of a Black patient.



Naked granulomas are characteristic of sarcoidosis and are composed of epithelioid histiocytes and multinucleated giant cells (black solid arrow). (Courtesy L. Coleman, MD.)

Acne rosacea

Clinical features: presents with erythematous papules and pustules, telangiectasia on central face.

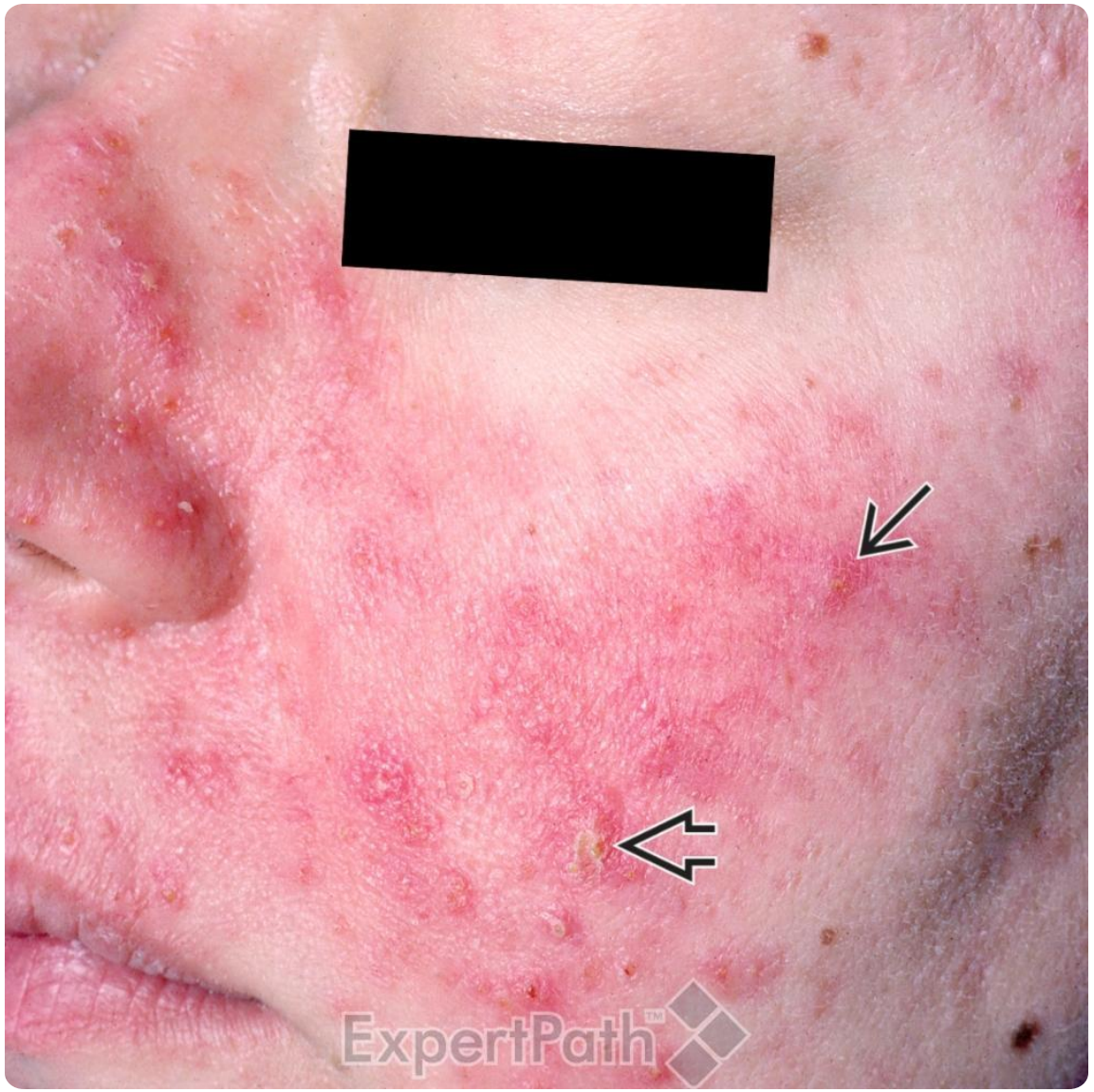
Advanced Form: Lewandowsky rosacea presents as yellow-brown nodules.

Histopathology:

- Mixed perivascular and perifollicular inflammation with lymphocytes, plasma cells, macrophages.
- **Pustular Lesions**: Increased neutrophils, termed pyoderma faciale or rosacea fulminans.
- Prominent perifollicular neutrophils.

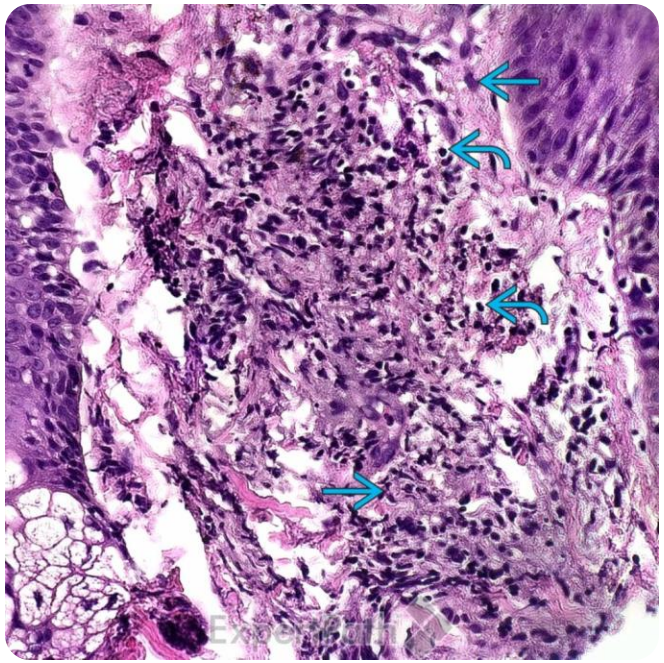
Differential diagnosis:

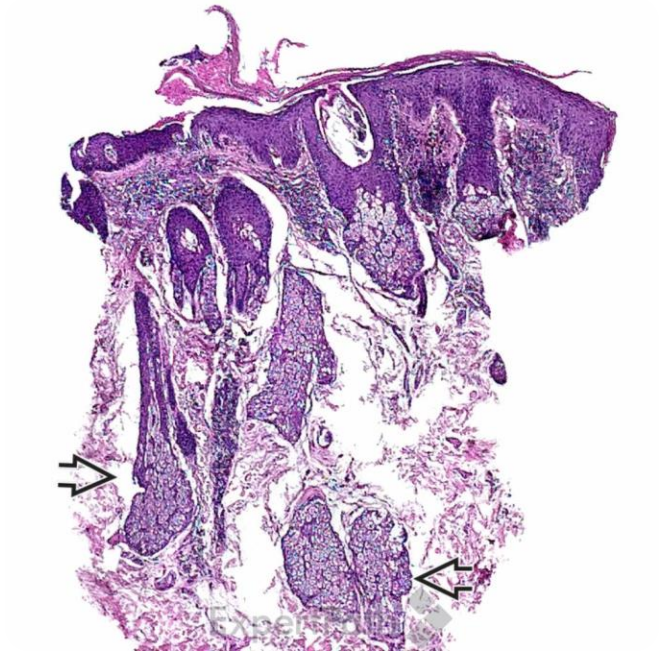
- Lupus miliaris disseminatus faciei
- oral facial granulomas
- perioral dermatitis
- Crohn's disease, sarcoidosis
- lupus vulgaris (skin tuberculosis)
- CTCL
- NK/T-cell lumphoma



Acne rosacea

- Papulopustular rosacea is characterized by erythematous papules (black solid arrow) that may be topped by pustules (black open arrow). There is also marked skin edema, which causes skin to feel hard or solid.



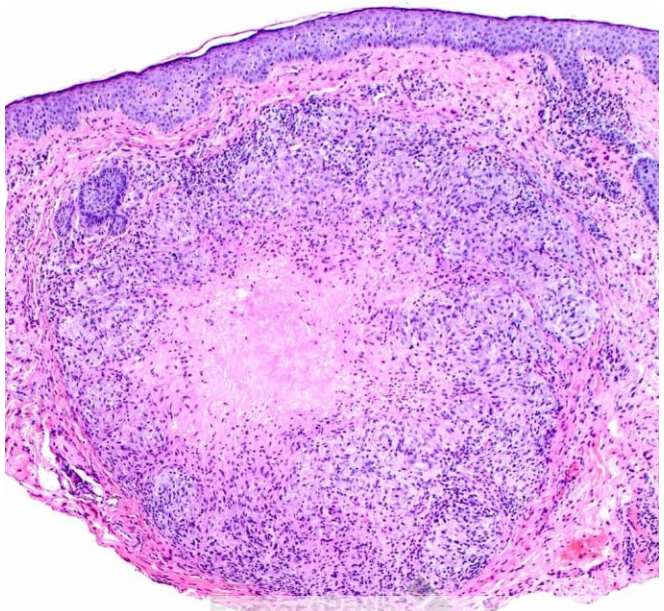


Acne rosacea

High-power: perifollicular infiltrates and ill-defined granuloma, consisting of histiocytes (cyan solid arrow) and lymphocytes (cyan curved arrow).

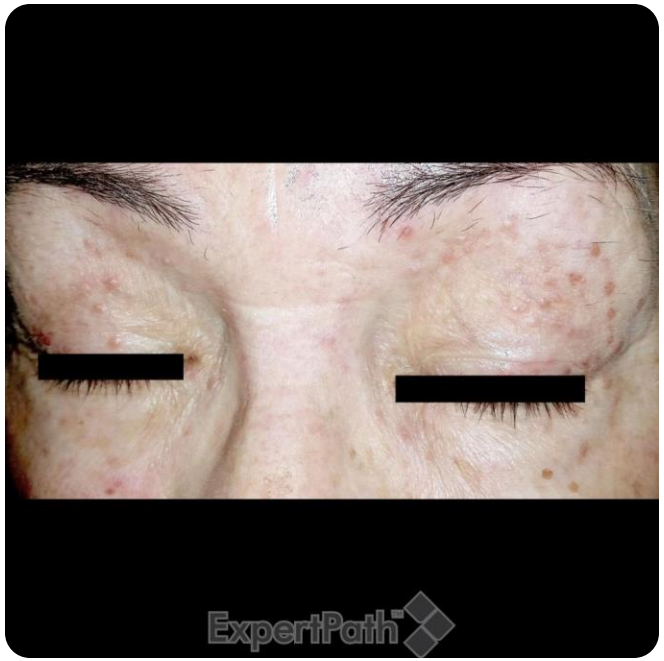
Low-power: hyperplasia, as the concentration of sebaceous glands (black open arrow) is higher than usual.

Lupus Miliaris Disseminatus Faciei



Mature lesion of lupus miliaris disseminatus faciei shows an epithelioid granuloma with central necrosis. (Courtesy L.M. Bull, MD.)

- **Clinical Features:**
  - Dramatic form of granulomatous stage of acne rosacea
  - Yellow-brown papules on central face, typically involving eyelids
- **Histopathologic Features:**
  - Identical to granulomatous acne rosacea
  - May show caseation necrosis



Clinical photo shows the typical reddish-brown, dome-shaped papules in a periorbital distribution. (Courtesy L.M. Bull, MD.)

Cheilitis Granulomatosa (Miesher Melkersson Rosenthal Syndrome)

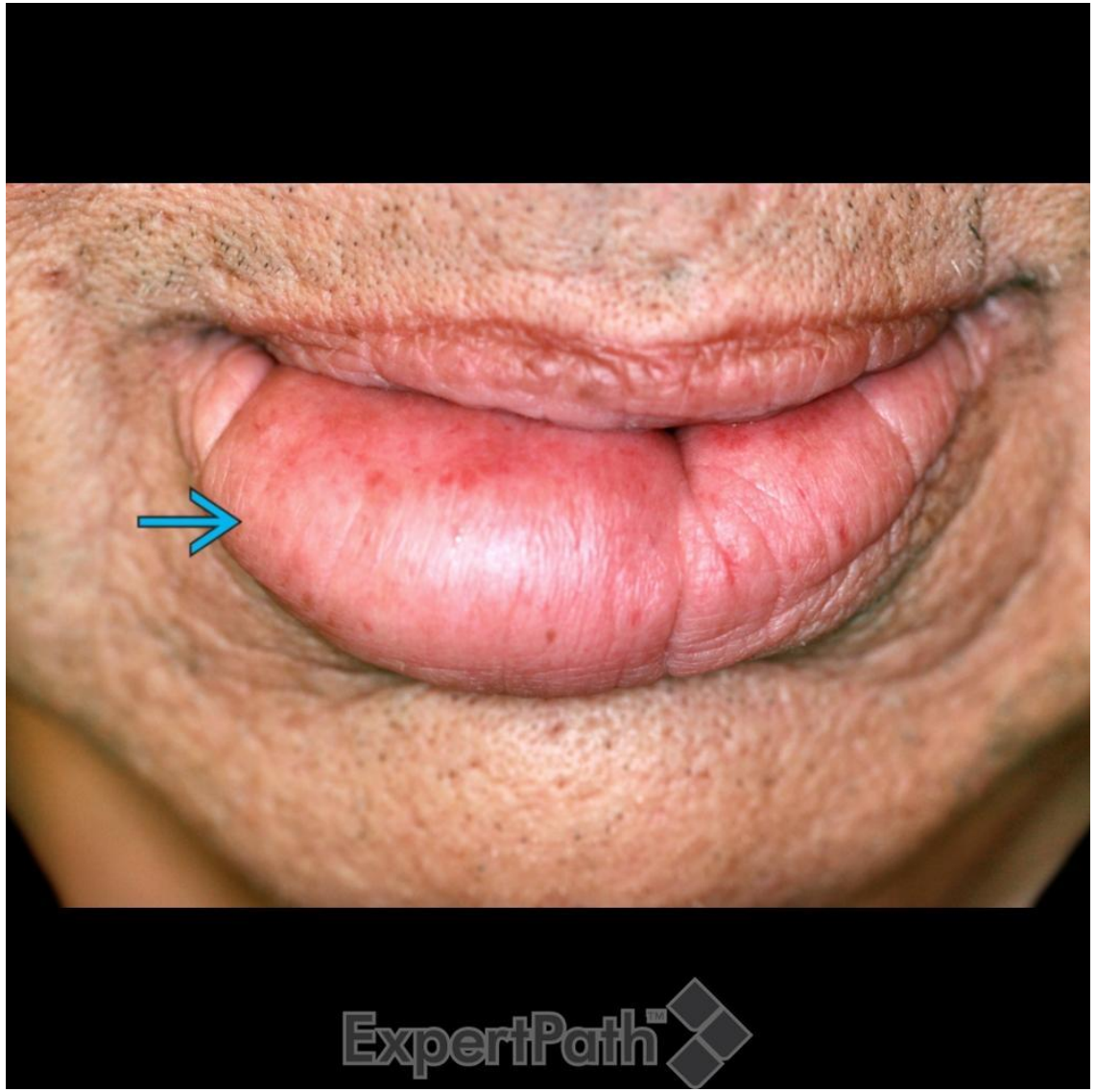
Clinical Features: Triad of lip swelling, unilateral facial paralysis, furrowed tongue.

Differential Diagnosis: Includes oral facial granulomas, acne rosacea, perioral dermatitis, Crohn's disease, sarcoidosis, lupus vulgaris (skin tuberculosis) , and other infections, chronic granulomatous disease.

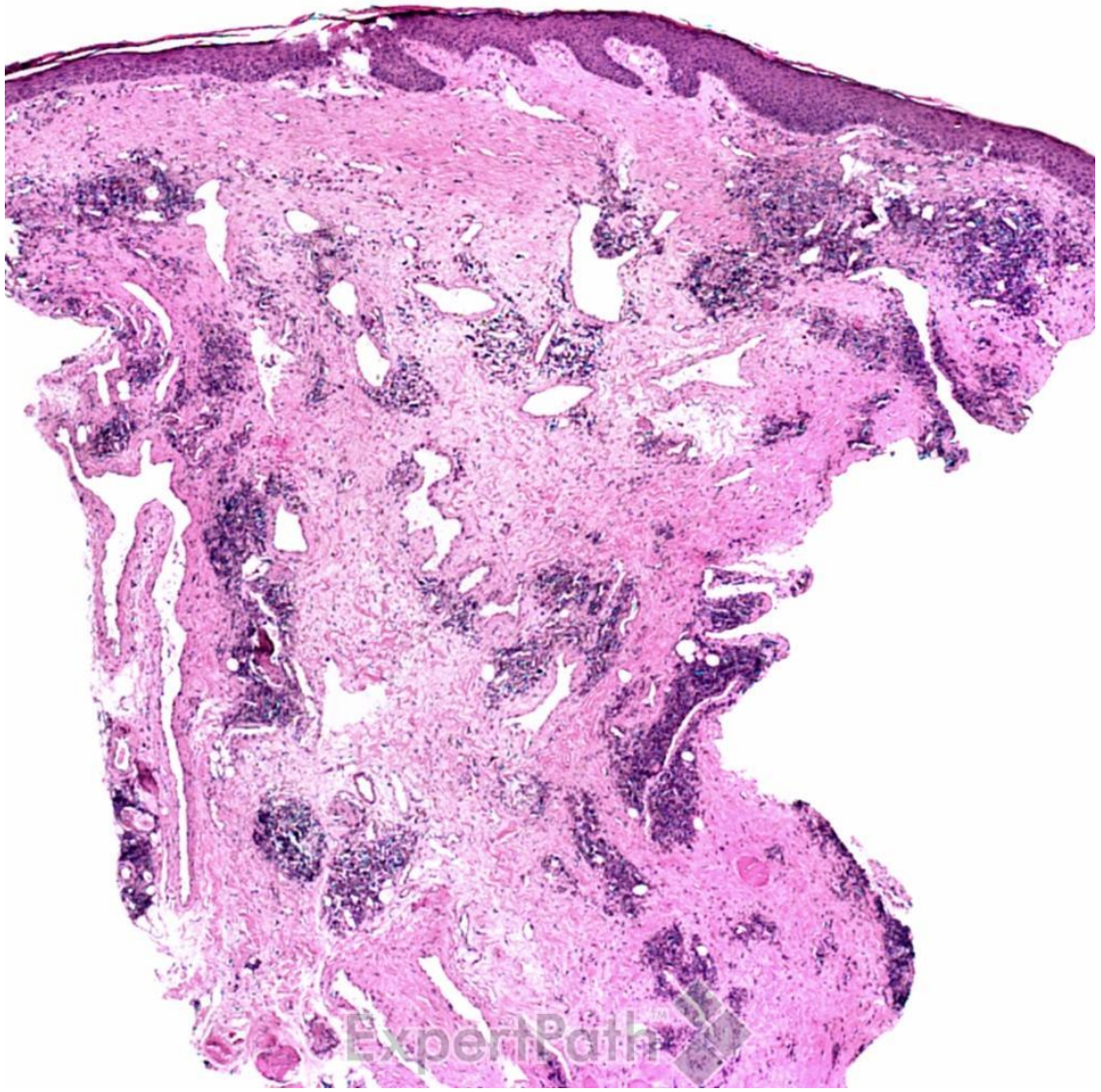
Histopathologic Features:

- Prominent dermal edema.
- Non-caseating poorly formed naked granulomas near dilated lymphatics.
- Perivascular lymphocytic and plasma cell infiltrate.

Cheilitis Granulomatosa (Miesher Melkersson Rosenthal Syndrome)



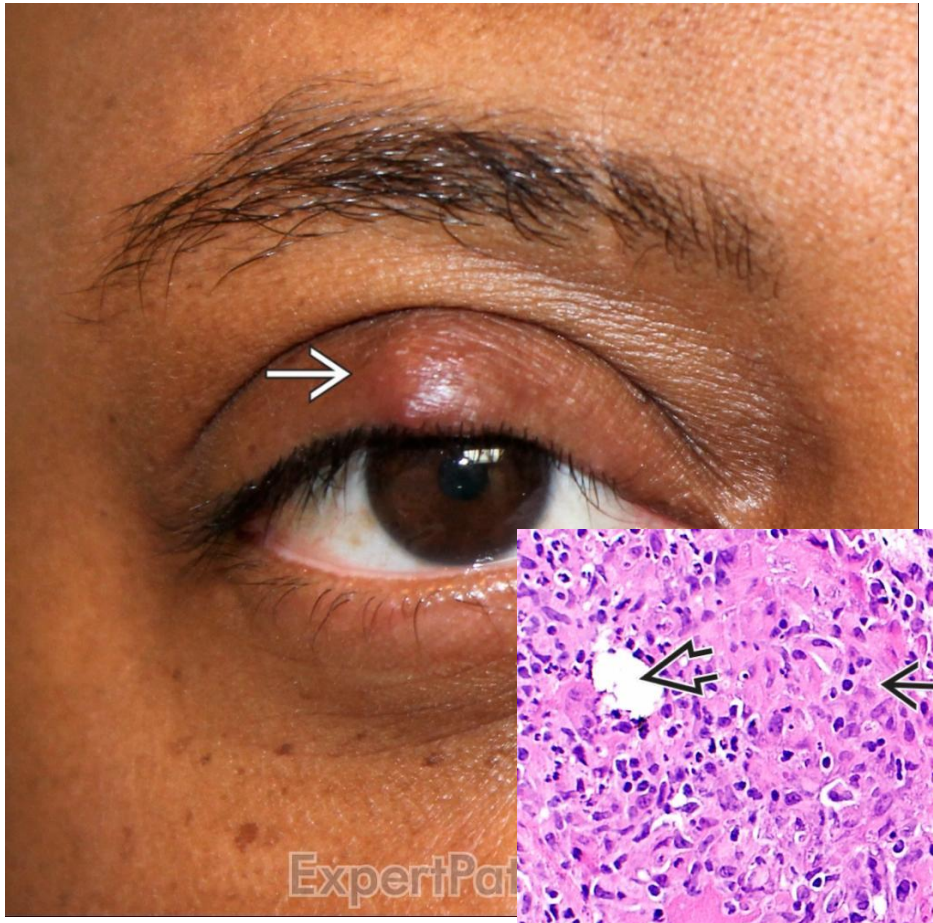
Chronic swelling of the lip (cyan solid arrow) is shown in a patient with cheilitis granulomatosa, which is part of Melkersson-Rosenthal syndrome (MRS).



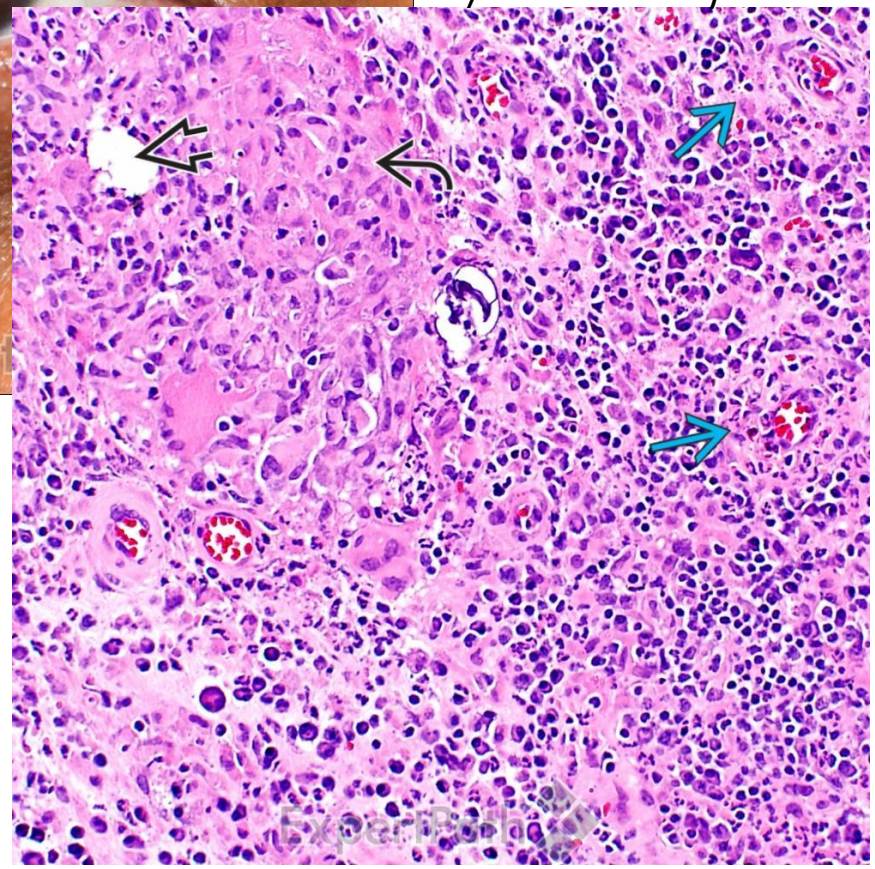
Low-power view of MRS shows a superficial and deep, perivascular, granulomatous, chronic inflammatory infiltrate and diffuse stromal edema.

Chalazion

- **Clinical Features:**
  - Nodules of the eyelid
  - Usually painless and solitary
- **Histopathologic Features:**
  - Nodular infiltrate with lymphocytes, plasma cells, sometimes neutrophils
  - Non-caseating granulomas centered around lipid vacuoles or Meibomian glands



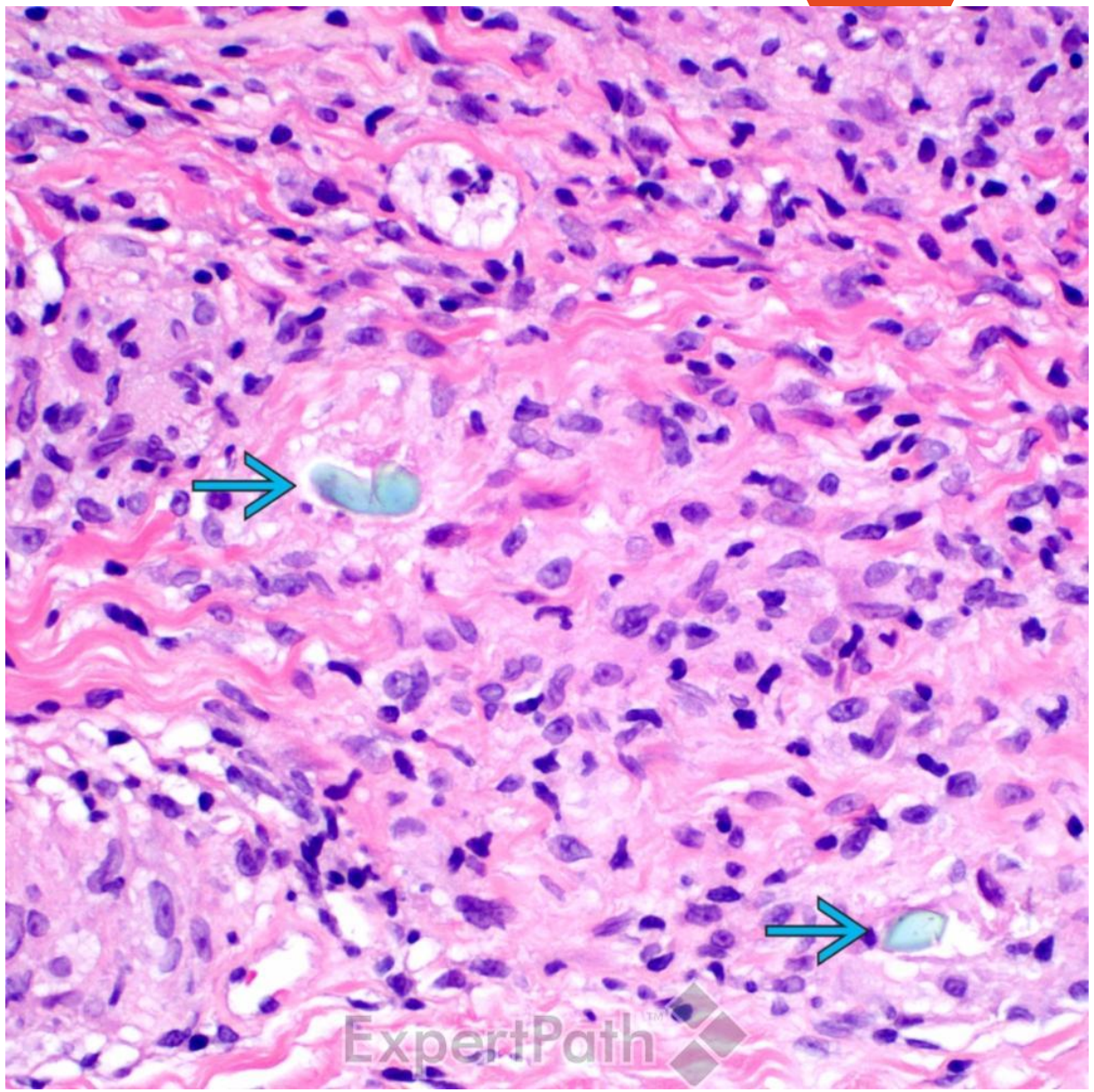
Chalazion (white solid arrow): patient's upper eyelid; higher density of meibomian glands on the upper lid. (Courtesy Moran Eye Center.)



Chronic granulomatous inflammation is embedded in granulation tissue (cyan solid arrow). Note the fat droplet (black open arrow) in the center of a granuloma (black curved arrow). This a common feature of chalazia.

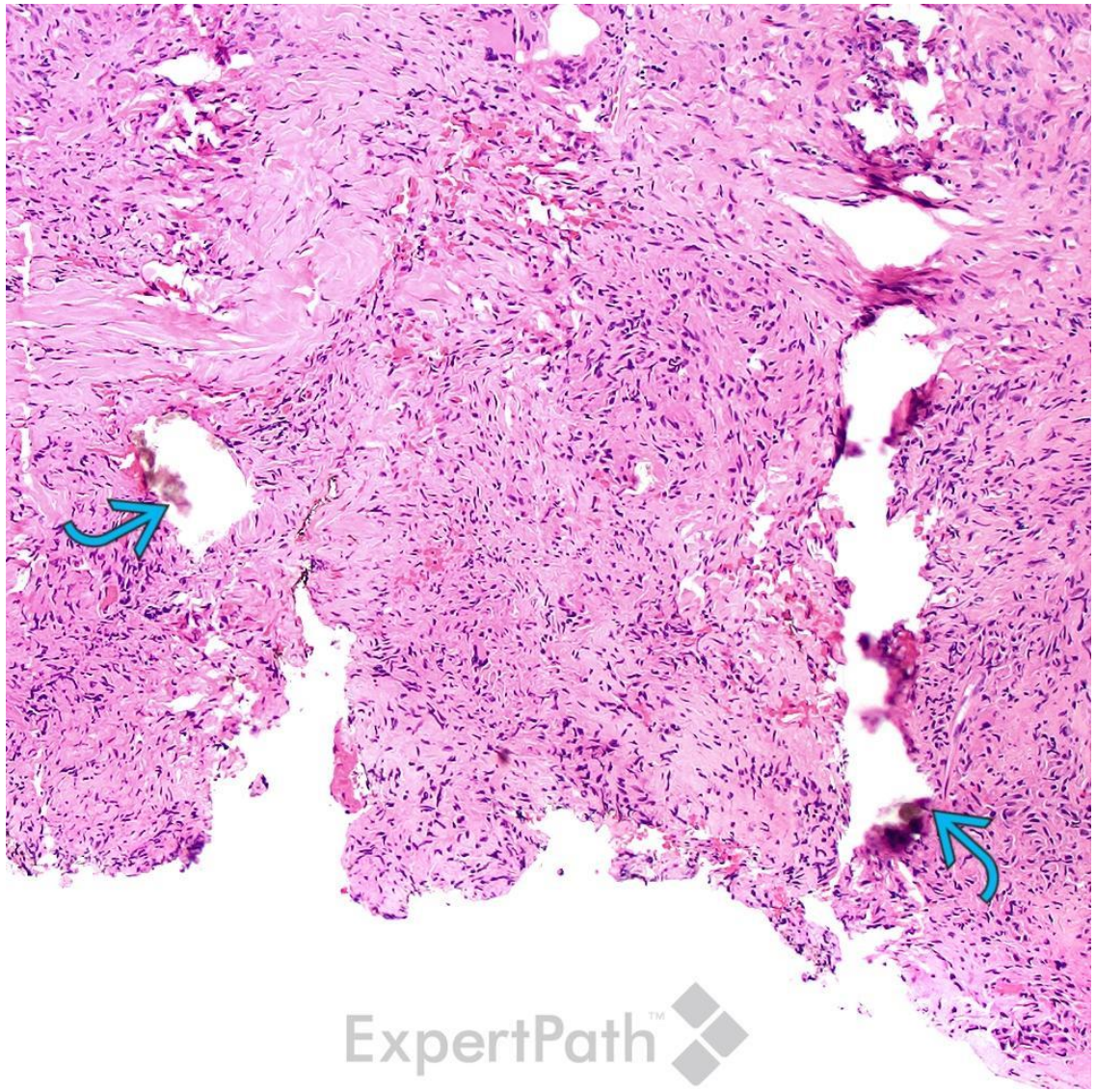
Foreign Body Granulomas

- **Clinical Features:**
  - Forms around endogenous or exogenous material contacting the dermis
- **Histologic Features:**
  - Multinucleated giant cells with nuclei conglomerated centrally or at cell edges
- **Differential Diagnosis:**
  - Sarcoidosis

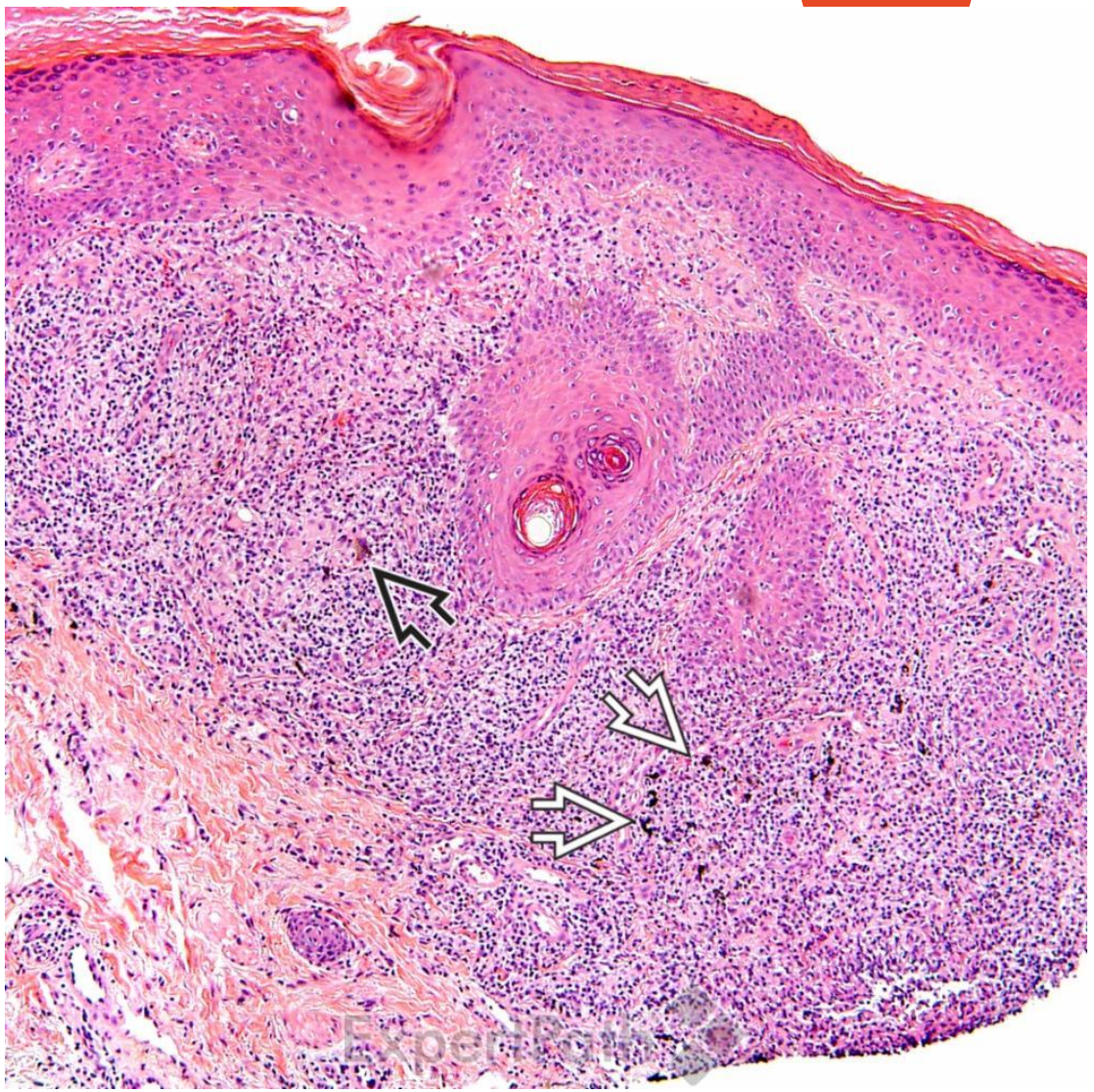


Sarcoidal granulomatous dermatitis surrounds several small fragments of blue-green foreign material (cyan solid arrow).

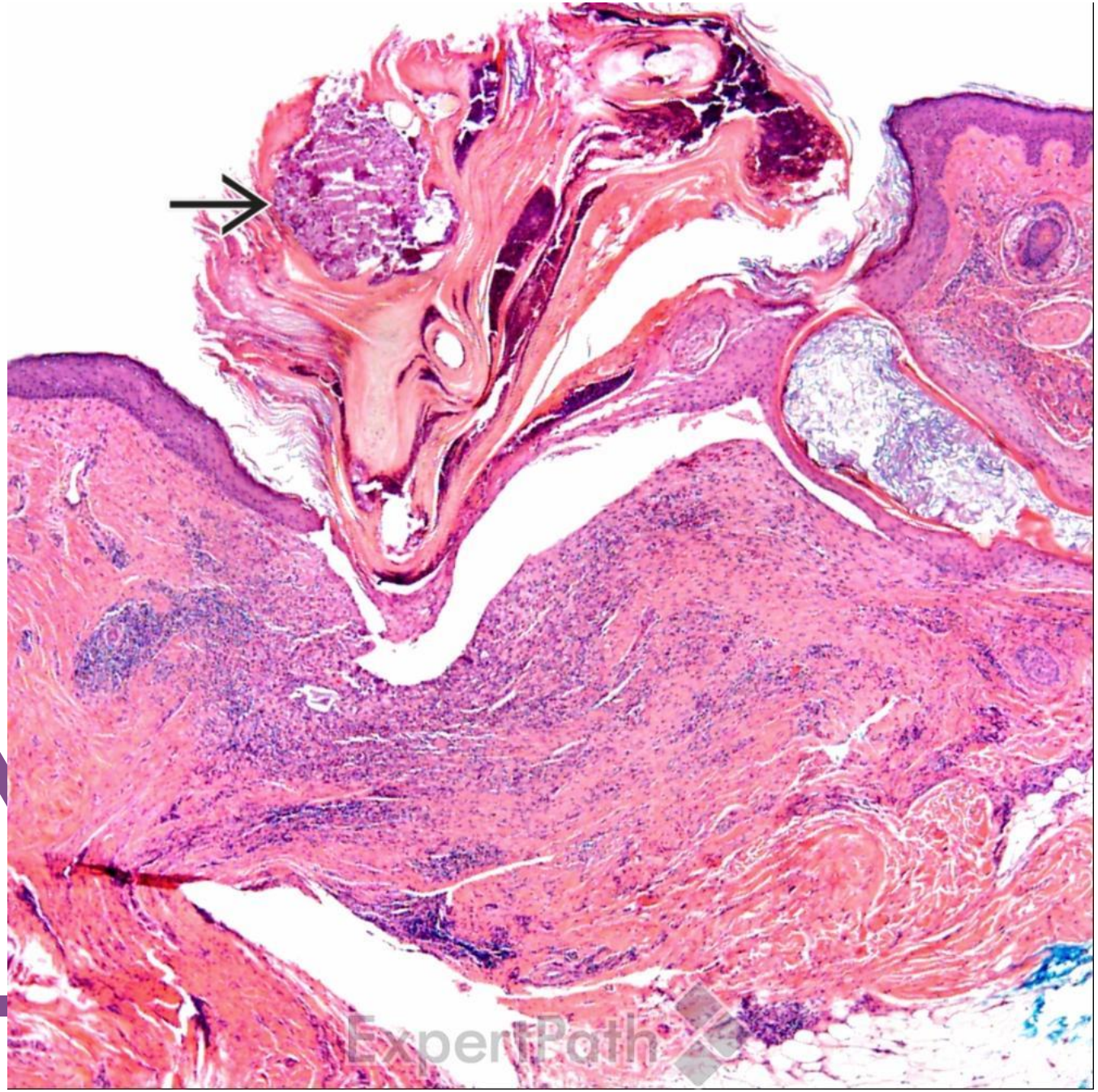
Foreign body granuloma



Toward the base of this specimen, foreign material (cyan curved arrow) is evident as the reason for the scoring lines, as the histology blade scraped the foreign material through the tissue. Background histiocytic inflammation is present.



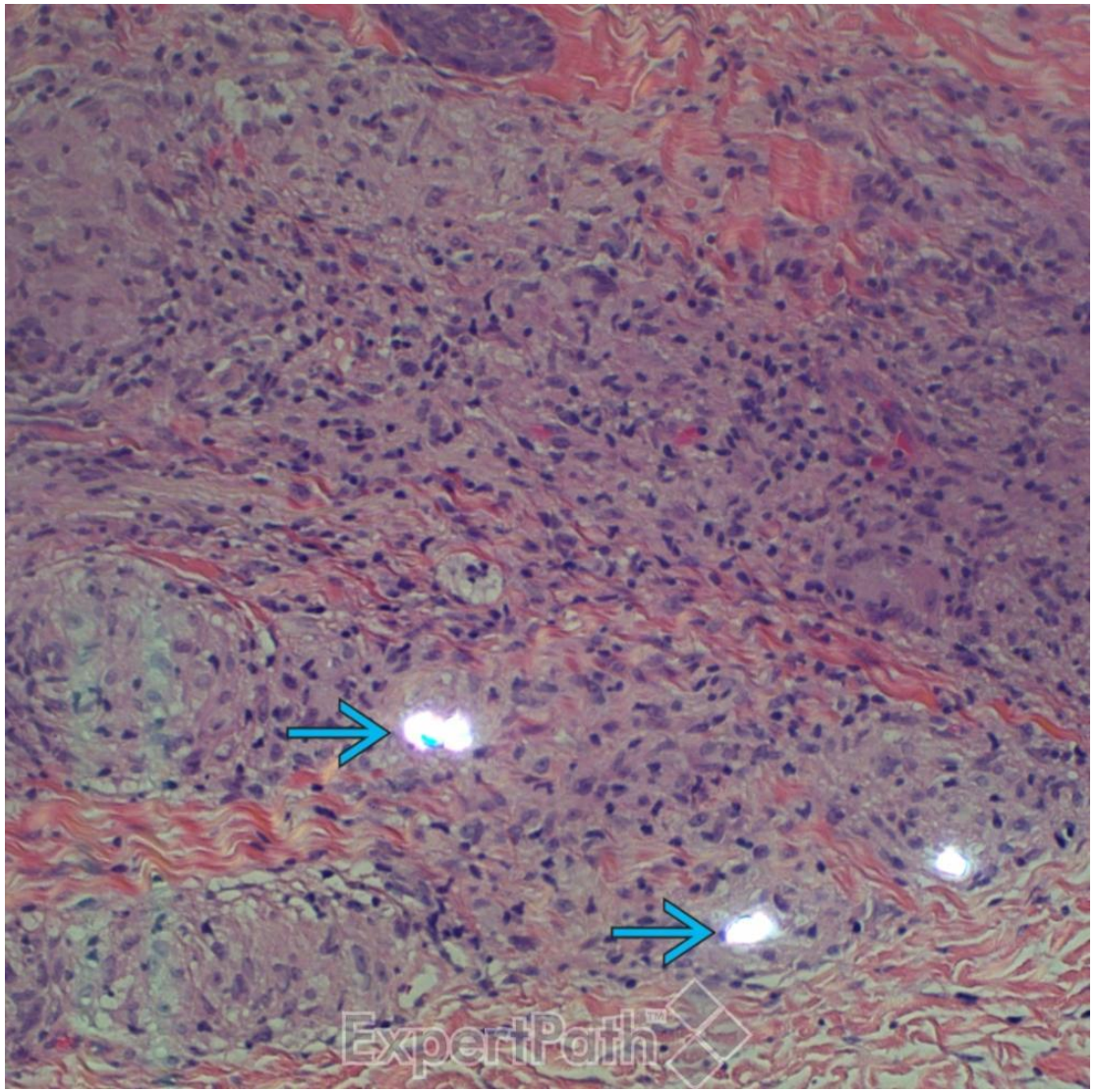
FBG in response to tattoo pigment shows a florid dermal granulomatous inflammatory response with occasional giant cells (black open arrow) and ink (white open arrow) being ingested by macrophages. (Courtesy L. Coleman, MD.)



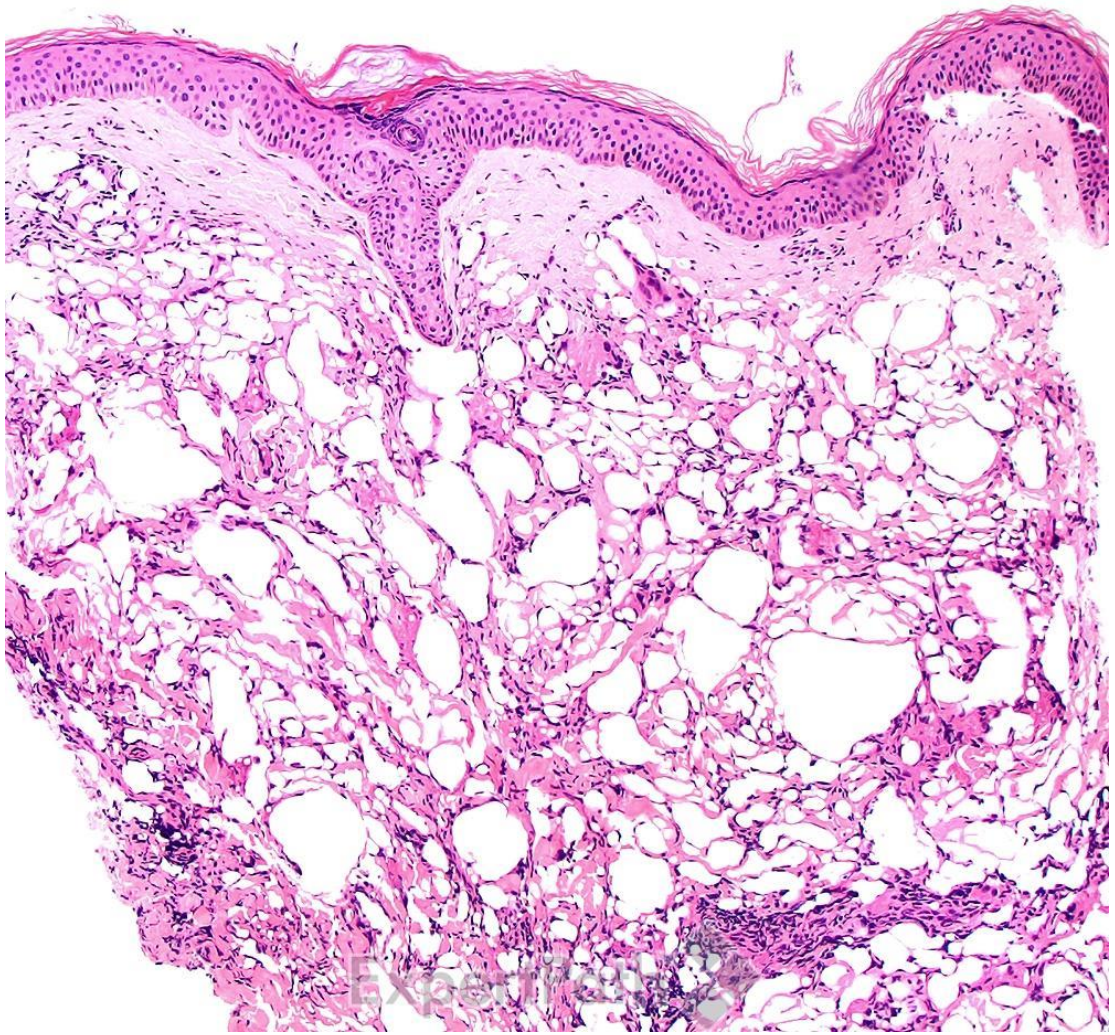
Foreign body granuloma with perforation

FBG can mimic a perforating dermatosis on low power. Suture material (black solid arrow) was easily identifiable as the cause in this case. (Courtesy L. Coleman, MD.)

Foreign body granuloma



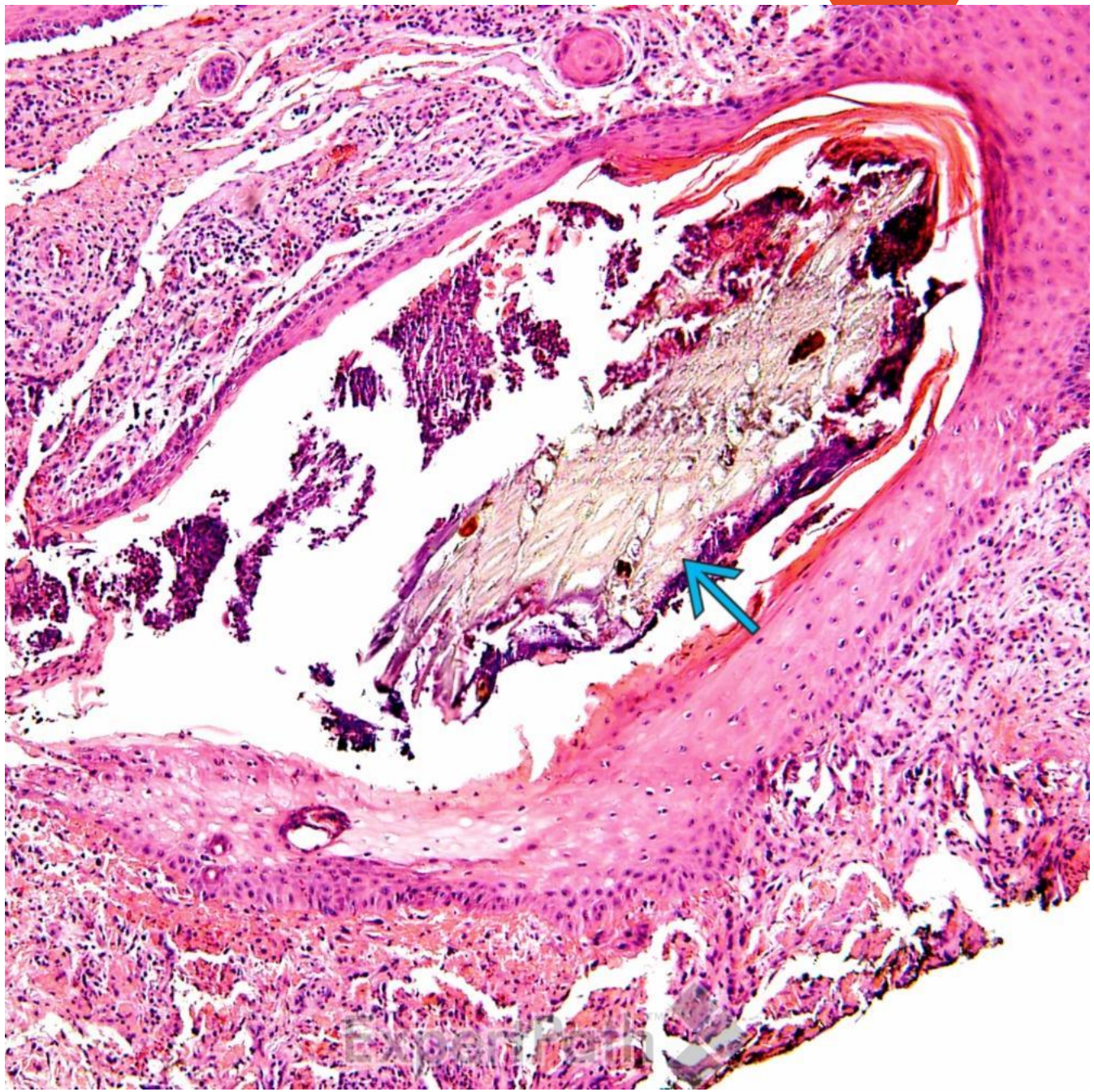
Polarizing microscopy confirms the presence of foreign material when refractile, acellular fragments are seen (cyan solid arrow).



In a silicone granuloma, a Swiss cheese pattern is seen within the tissue. Silicone does not polarize, so clinical correlation is necessary to confirm a silicone implant was in the vicinity of the biopsy specimen.

Foreign body granuloma to wood splinter

High-power view shows FBG due to a wood splinter (cyan solid arrow). Note how the skin is walling off the foreign body so that it can eventually be extruded. (Courtesy L. Coleman, MD.)



Palisaded granulomatous infiltrates: granuloma forms an enclosure around necrobiosis (altered collagen)

Granuloma Annulare

Clinical Features:

- Affects mainly children and young adults, but can occur at any age
- Localized erythematous, skin-colored papules in annular or polycyclic configurations
- Mainly on dorsal surfaces of hands, feet, arms, legs

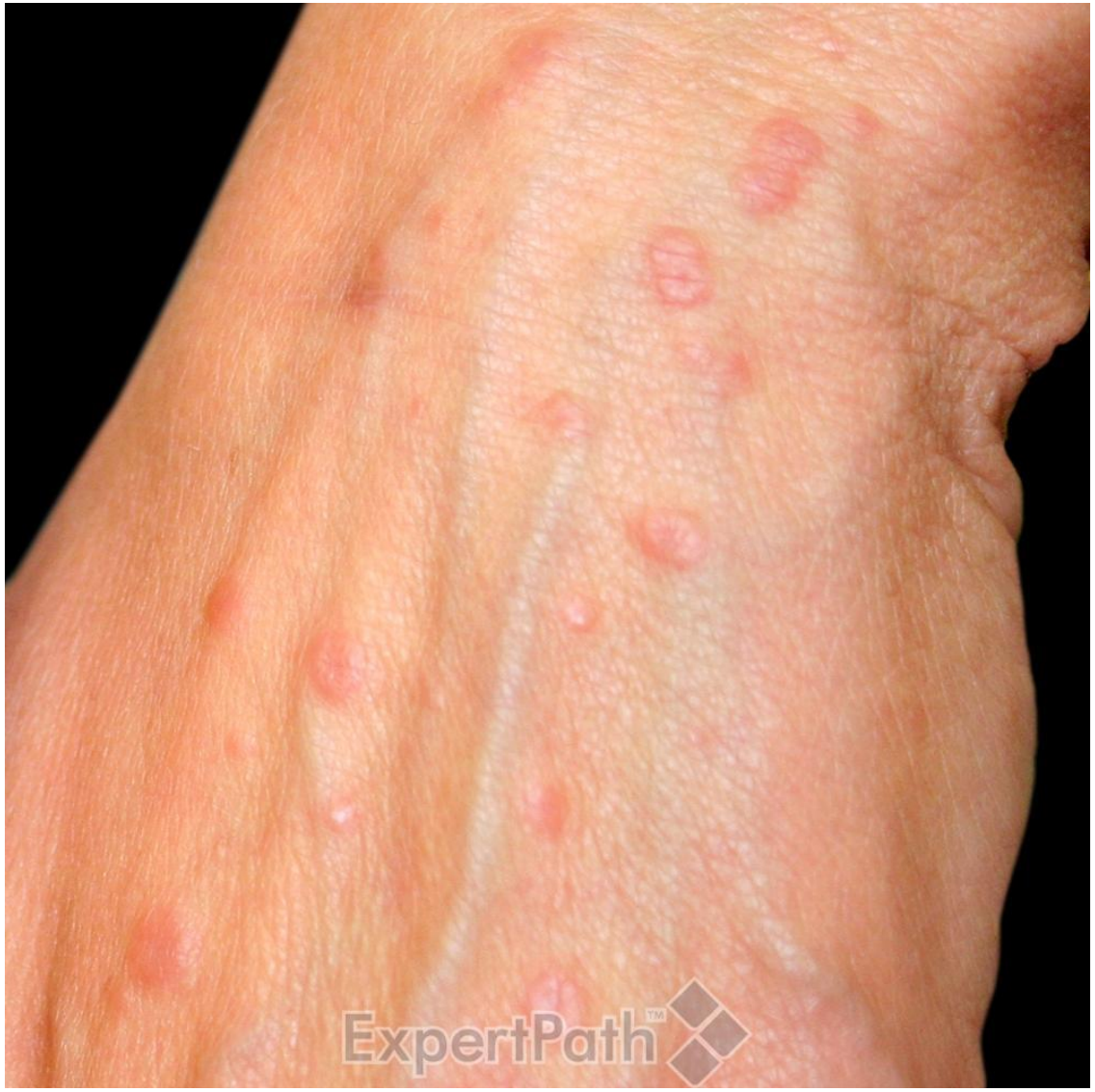
Histopathologic Features:

- Early lesions show tissue macrophages between collagen bundles
- Developed lesions have well-formed palisading granulomas with central mucin and degenerated collagen

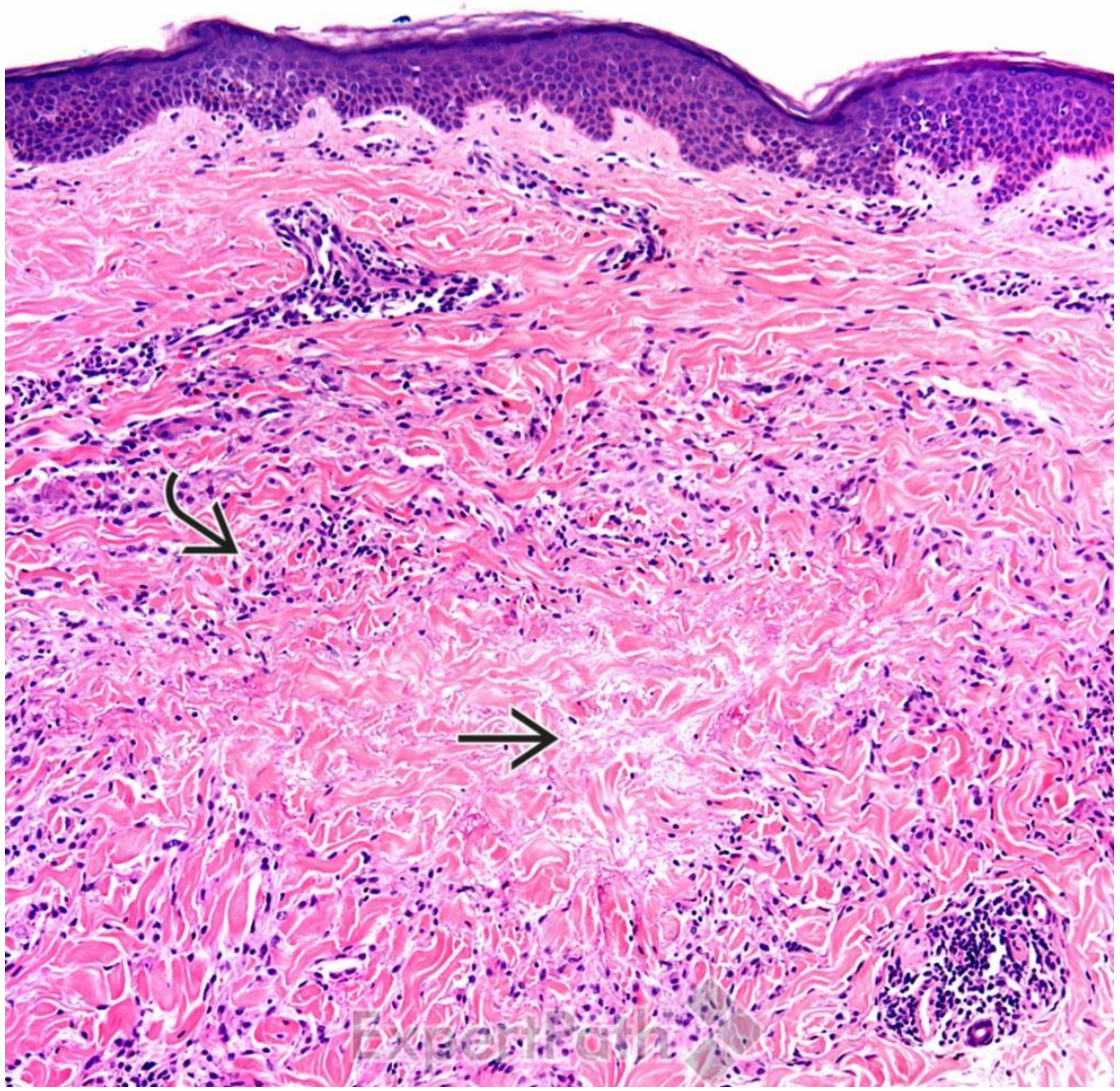
Differential Diagnosis:

- Necrobiosis lipoidica (NL) vs. Granuloma Annulare (GA):
  - NL often shows central collagen degeneration, lacks central mucin
  - GA's collagen is not altered and lacks plasma cells

Granuloma annulare

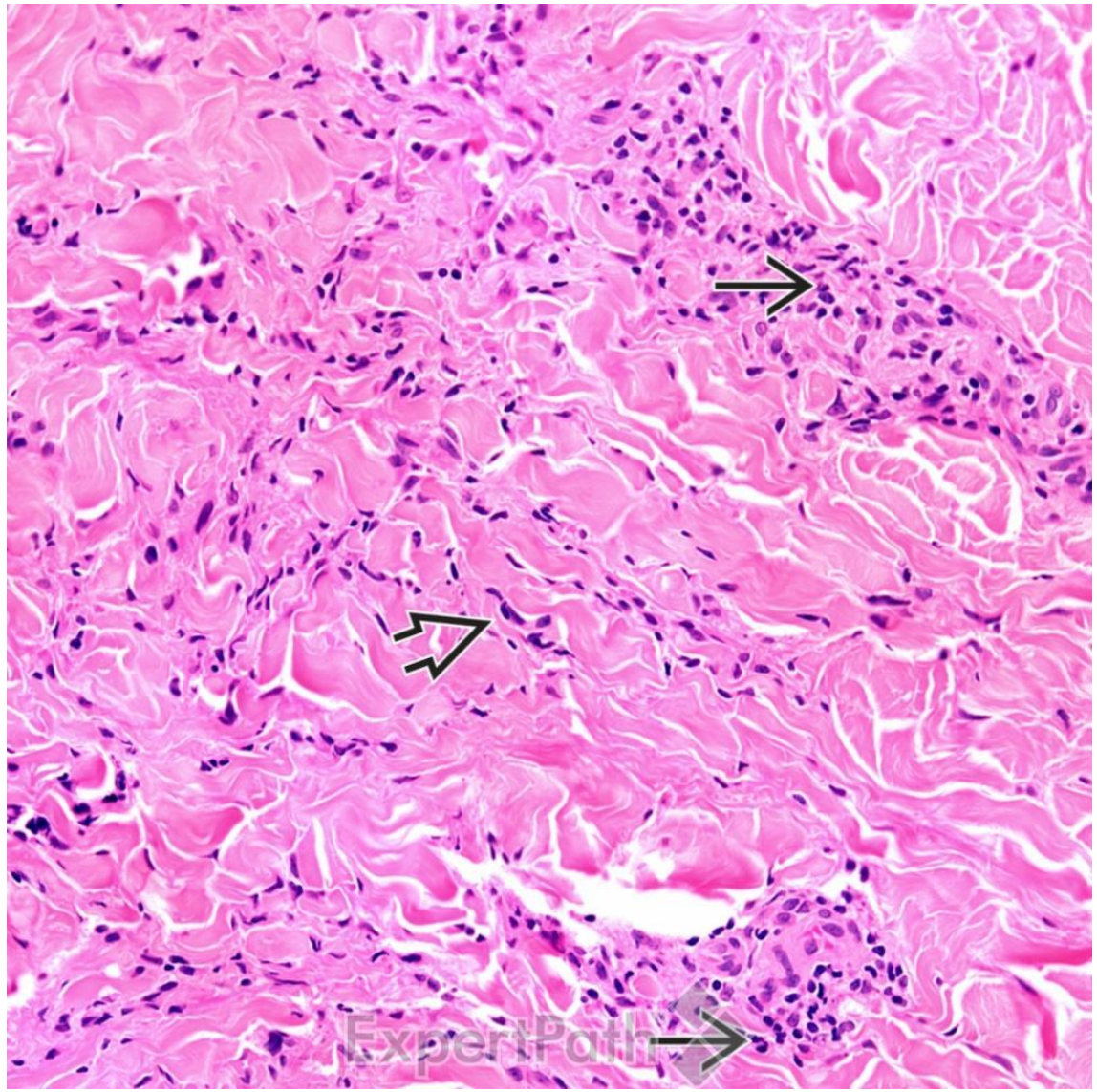


Clinical photo of granuloma annulare shows annular arrangements of pink papules on the dorsal hand. There is no surface scale. (Courtesy Yale Residents' Collection.)

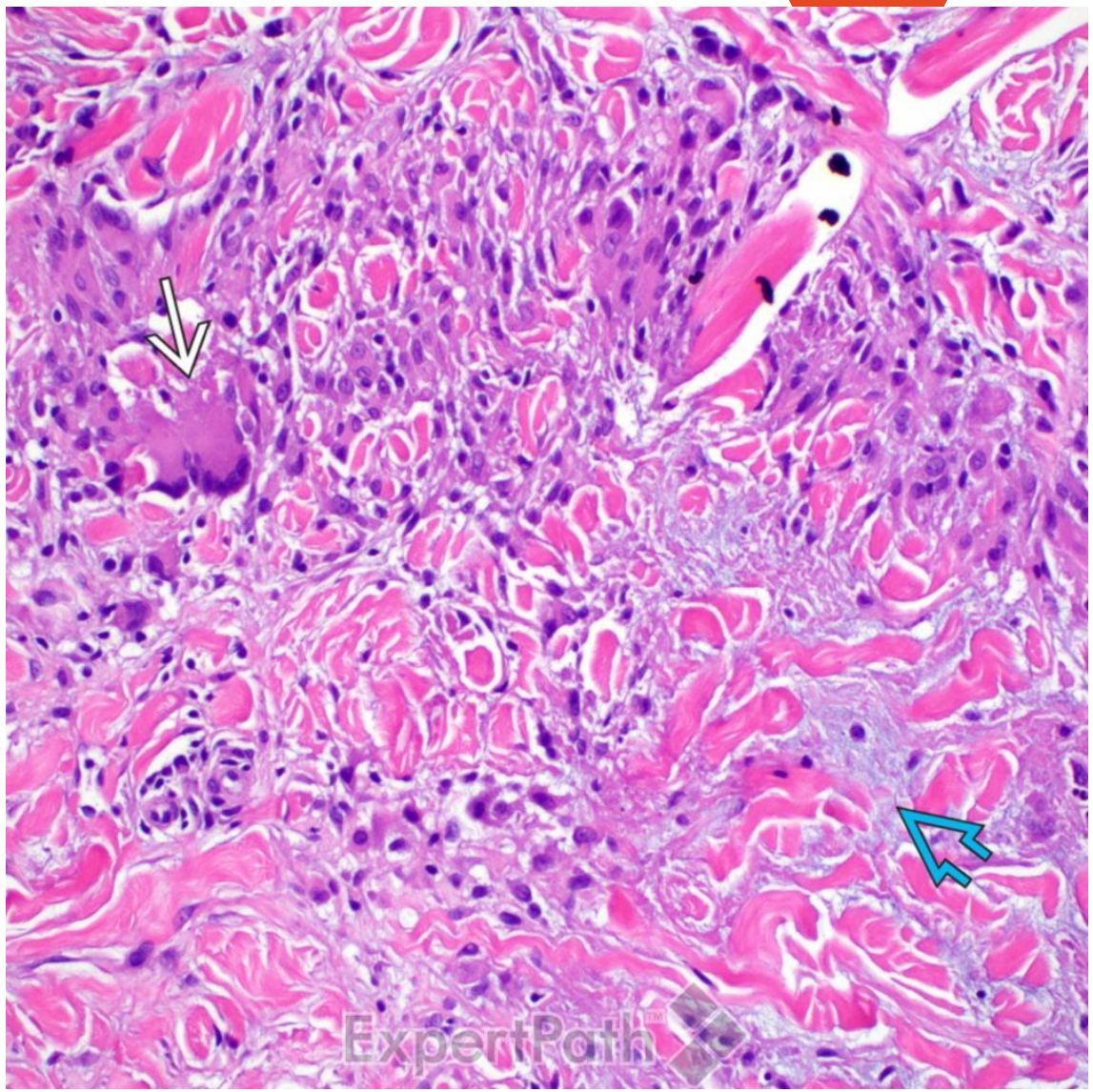


Granuloma annulare typically shows a palisade of histiocytes (black curved arrow) around central mucin (black solid arrow). There is a perivascular lymphocytic infiltrate.

Granuloma annulare



In the interstitial type of granuloma annulare, there are histiocytes (black open arrow) infiltrating between collagen bundles. Perivascular lymphocytic infiltrate (black solid arrow) is noted.



Histiocytes, including some multinucleate giant cells (white solid arrow), form a palisade around mucin (cyan open arrow) in the dermis.

Deep Granuloma Annulare

Clinical Features:

- Affects children more than adults
- Subcutaneous nodules on extensor aspects of hands, feet, lower legs, buttocks, scalp, periorbitally

Histopathologic Features:

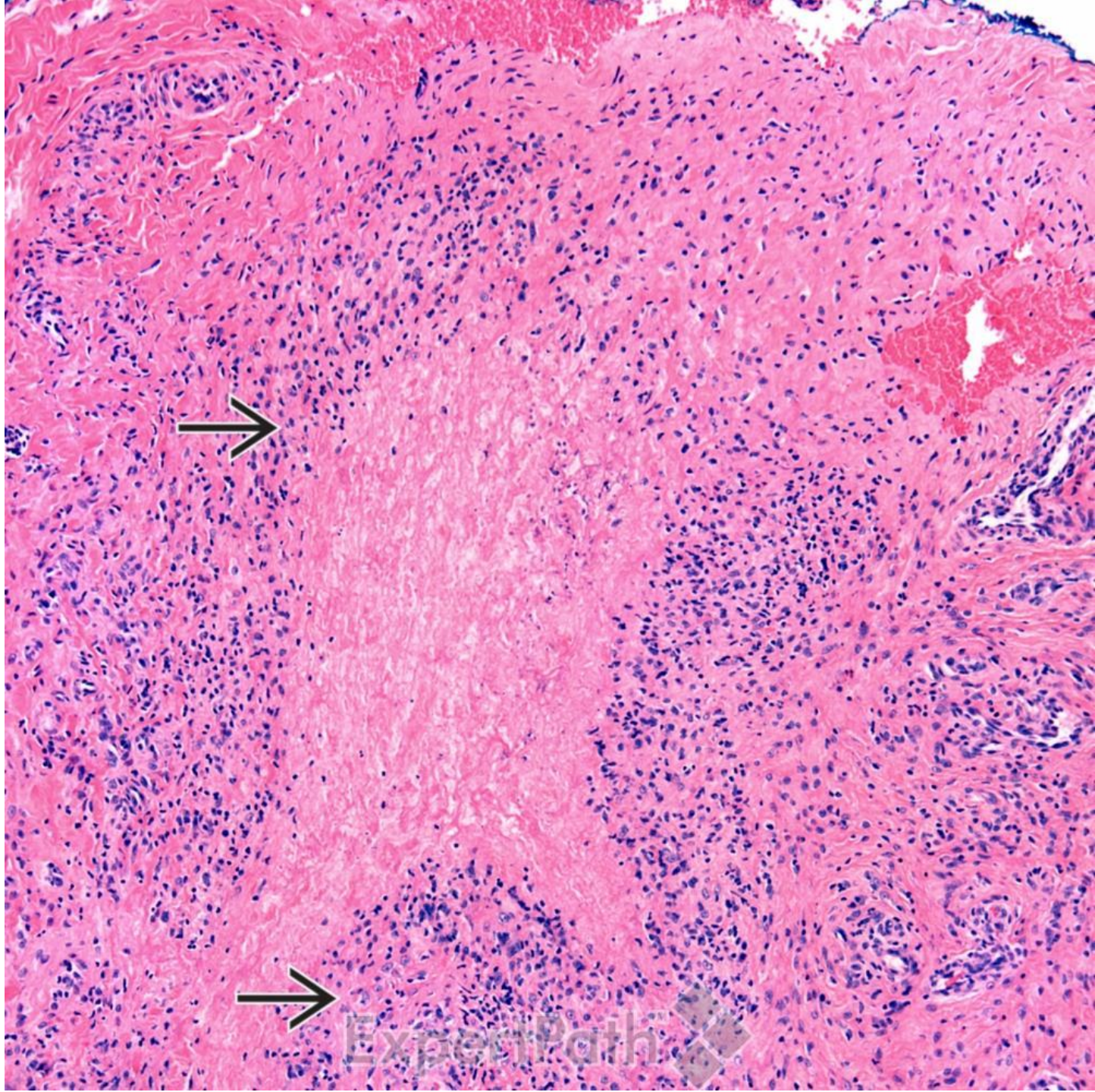
- Similar to superficial form but located deeper in dermis and subcutis

Differential Diagnosis:

- Rheumatoid nodule, rheumatic fever nodule, epithelioid sarcoma

Deep granuloma annulare

Deep granuloma annulare in subcutaneous tissue shows palisading of histiocytes (black solid arrow) around central mucin.



Actinic Granuloma

Clinical Features:

- Adults with expanding arceiform papules and plaques on face, sun-exposed areas

Histopathologic Features:

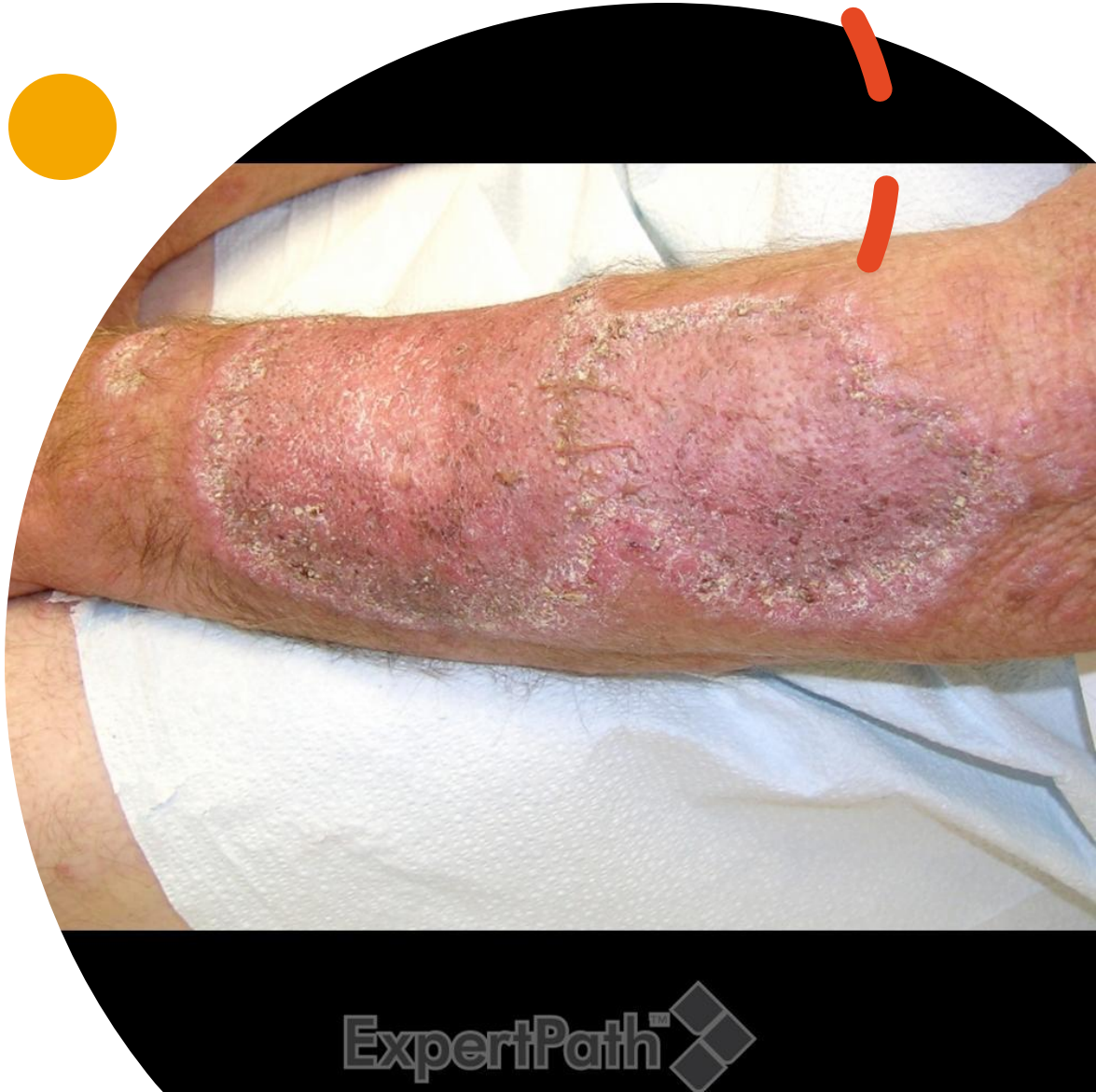
- Superficial dermis: Interstitial (incomplete) or palisaded peripheral (complete) macrophages around collagen bundles
- May contain blue-gray elastotic material, asteroid bodies

Differential Diagnosis:

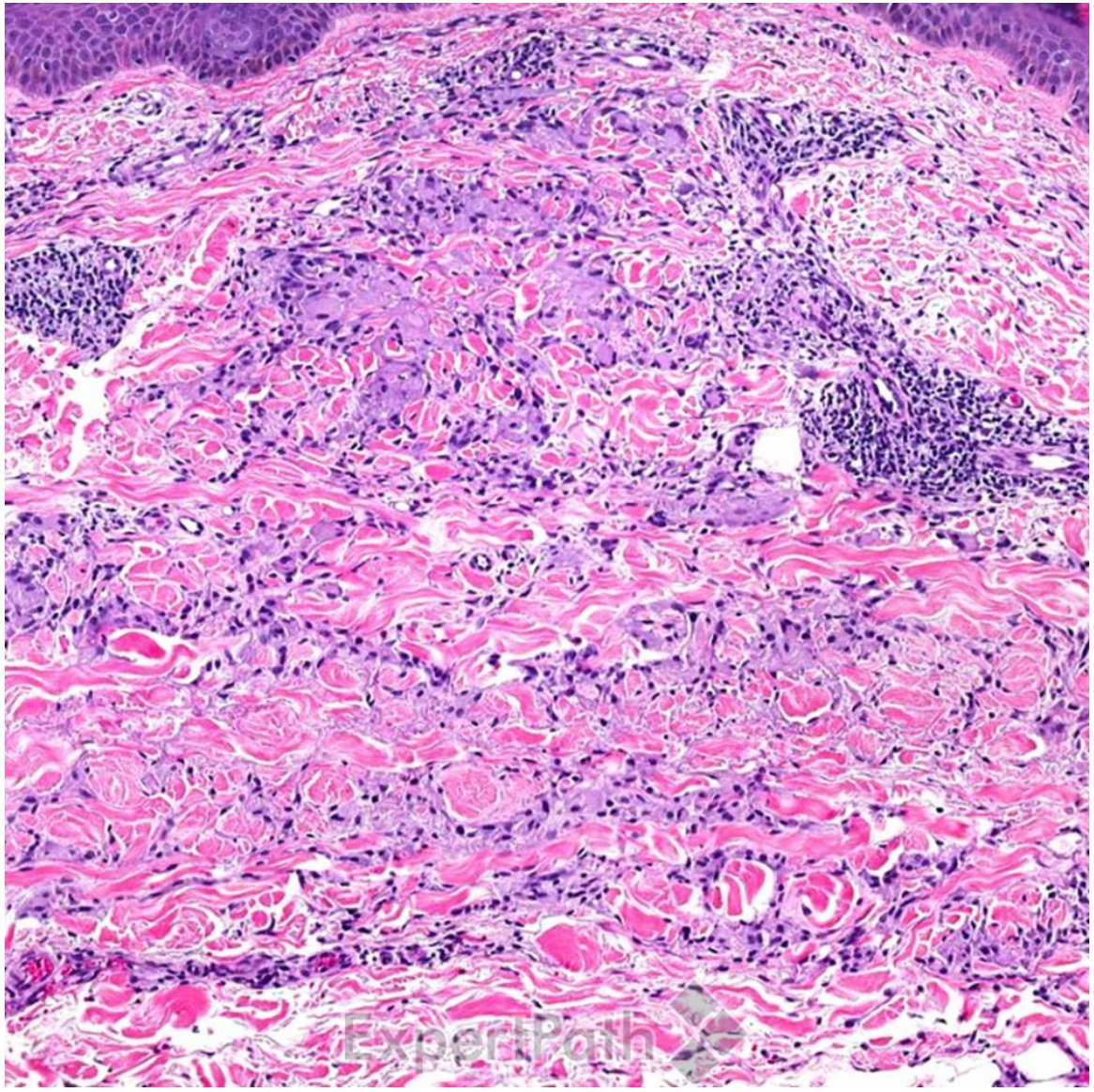
- Necrobiotic xanthogranuloma
- Granuloma annulare

Actinic granuloma

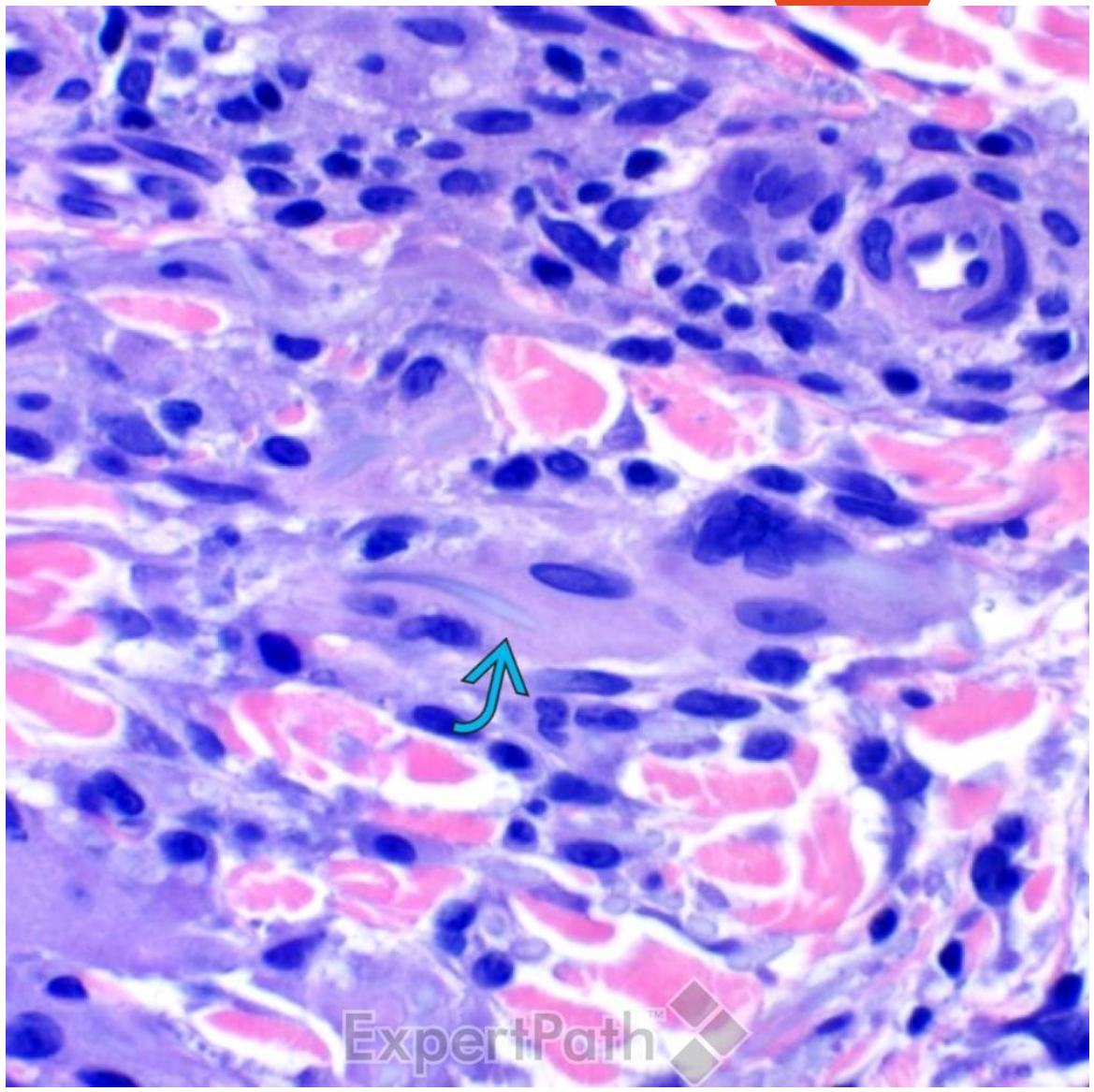
Actinic granuloma presents as annular plaques with atrophic centers and elevated borders on sun-exposed skin. (Courtesy S. Hsu, MD.)



Actinic granuloma



Interstitial granulomas are shown with numerous giant cells in classic actinic granuloma.



Elastophagocytosis in the second zone of actinic granuloma is shown. There is engulfment of elastotic fibers (cyan curved arrow) by multinucleate giant cells.

Necrobiosis Lipoidica

Clinical Features:

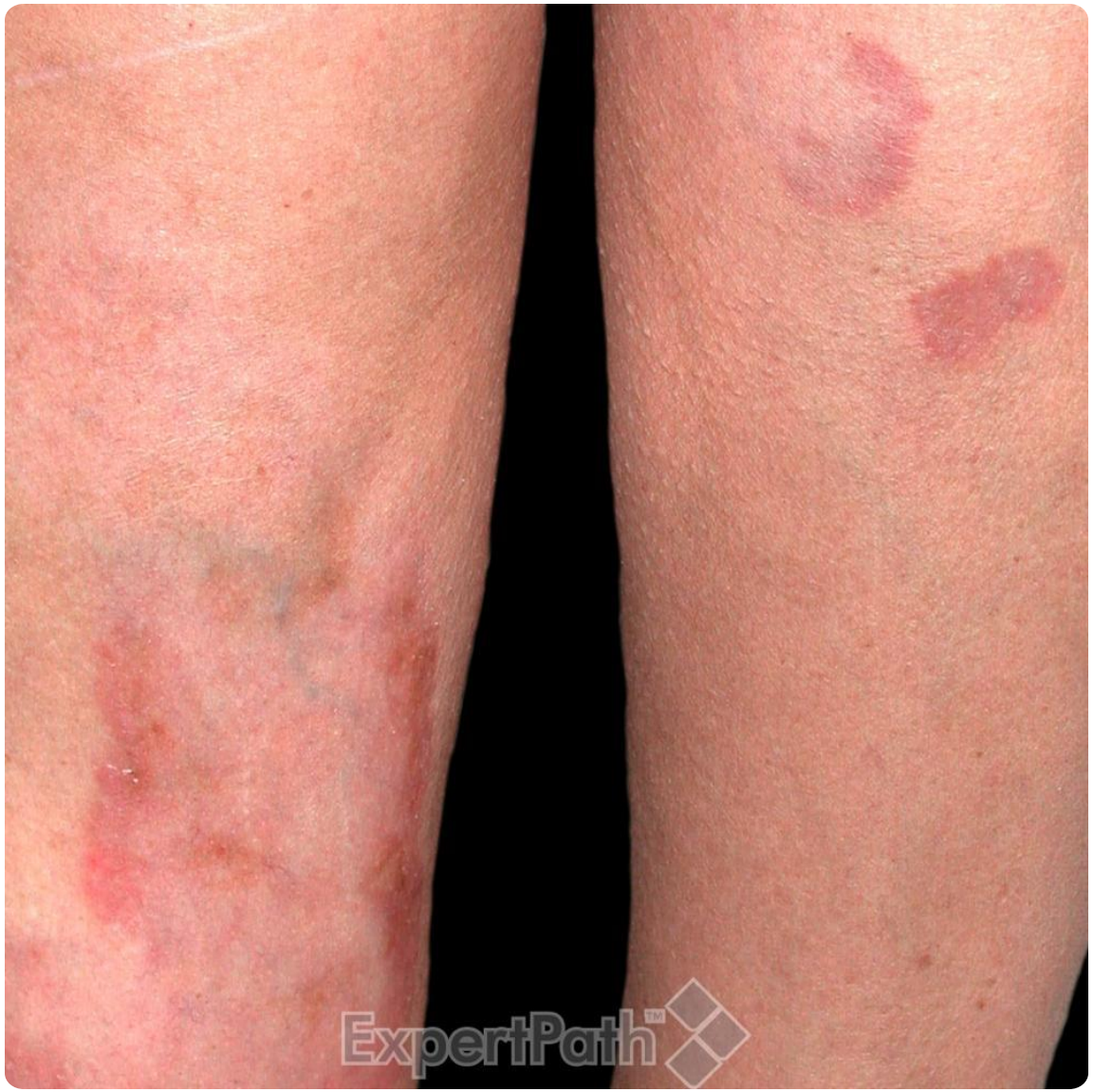
- Two-thirds of patients have diabetes mellitus
- Females affected more than males
- Waxy, indurated yellow-brown patches on anterior shins, forearms, hands, trunk

Histopathologic Features:

- Palisaded granulomatous infiltrate with degenerated collagen
- Plasma cells around deeper vessels

Differential Diagnosis:

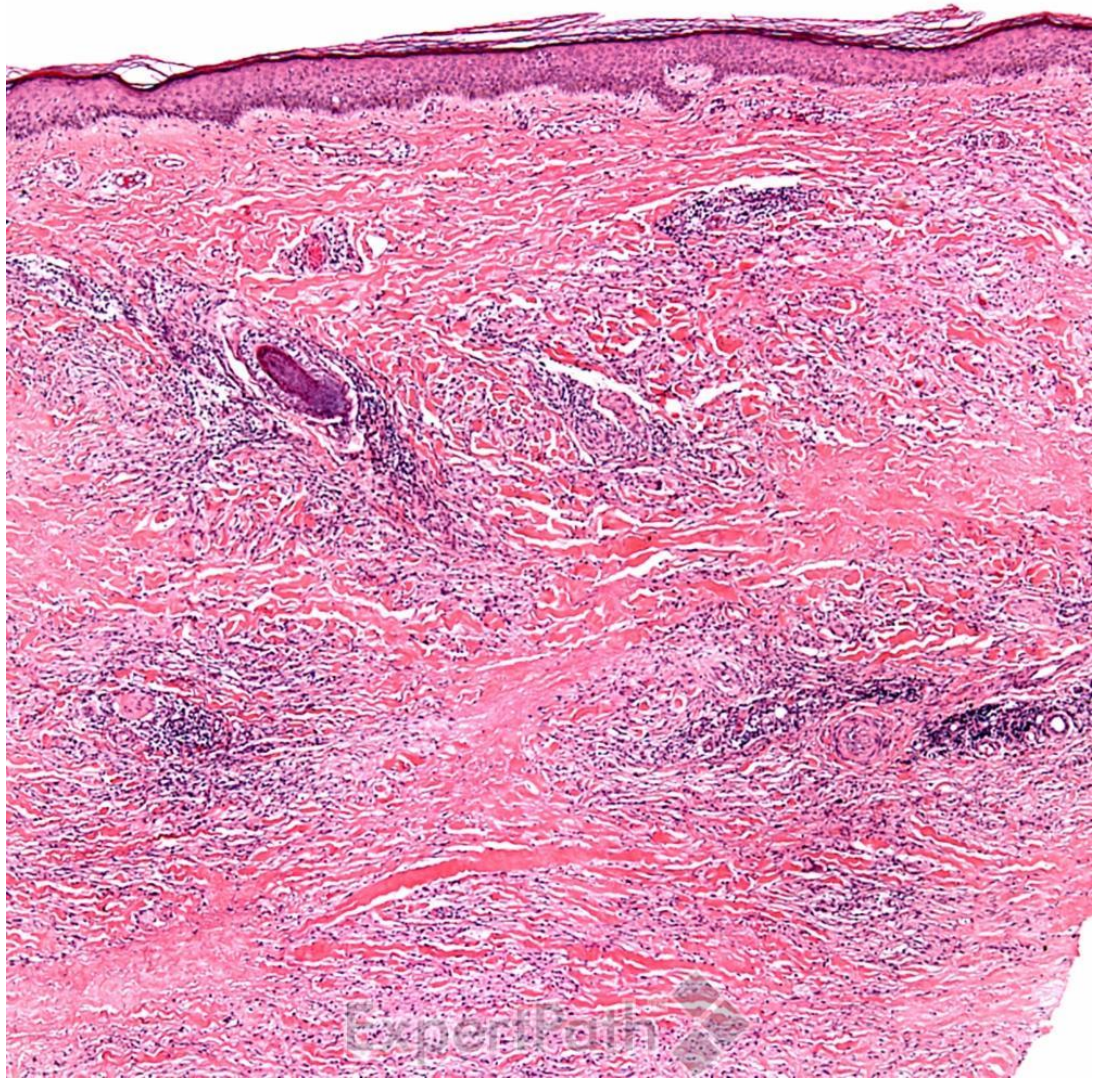
- Granuloma annulare
- Rheumatoid nodule



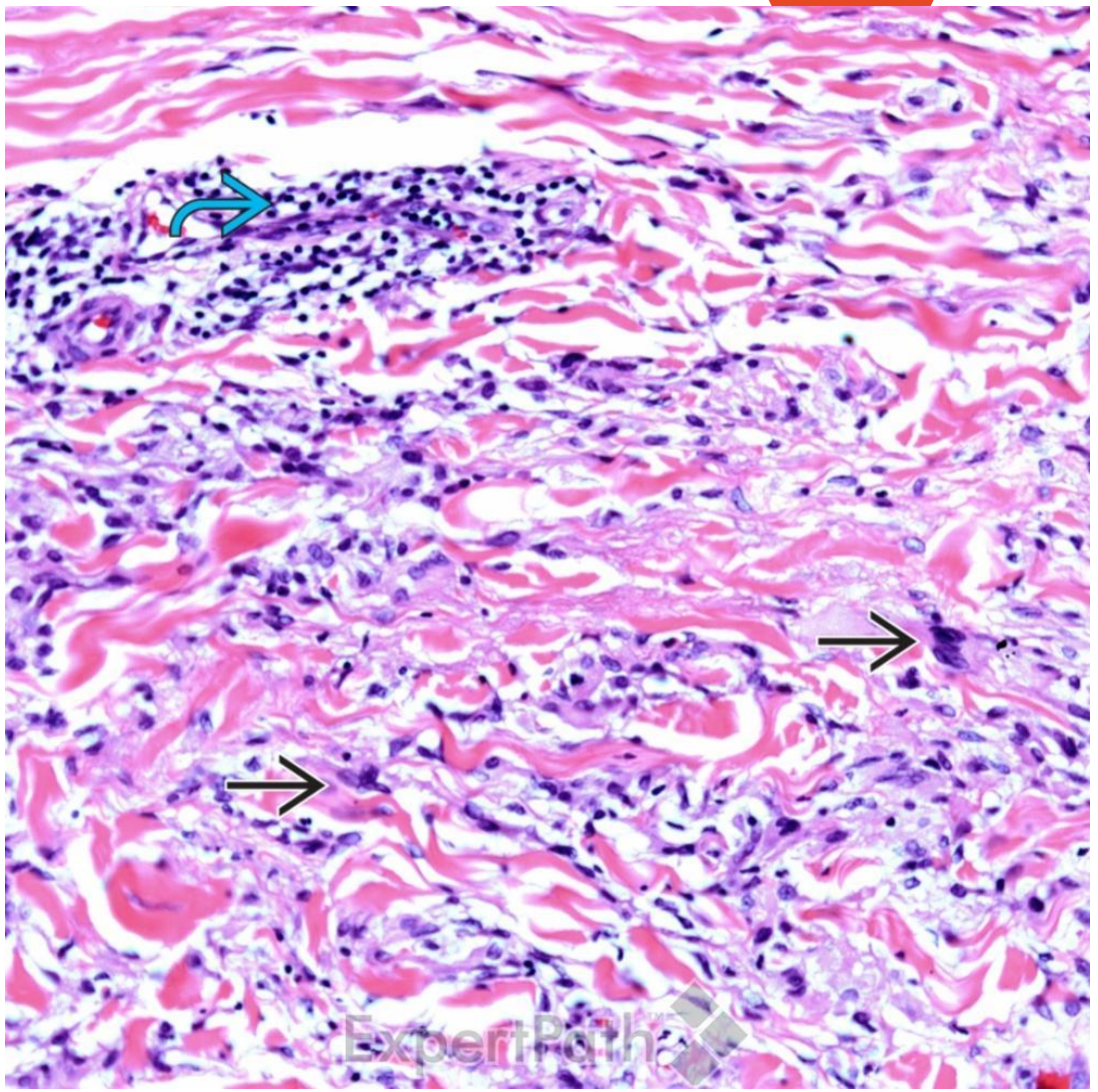
Necrobiosis lipoidica

Clinical photo shows lesions of necrobiosis lipoidica on shins. A larger plaque on the right shin has central atrophy. (Courtesy Yale Residents' Collection.)

Necrobiosis lipoidica



Necrobiosis lipoidica shows layers of altered collagen sandwiched between inflammatory cells. There is a perivascular lymphocytic infiltrate.



The inflammatory infiltrate in necrobiosis lipoidica consists of histiocytes, giant cells (black solid arrow), lymphocytes, and plasma cells sandwiched between layers of altered collagen. There is a perivascular lymphocytic infiltrate (cyan curved arrow).

Rheumatoid Nodule

Clinical Features:

- Seen in 20% of adults with rheumatoid arthritis
- Subcutaneous nodules on joints, especially elbows

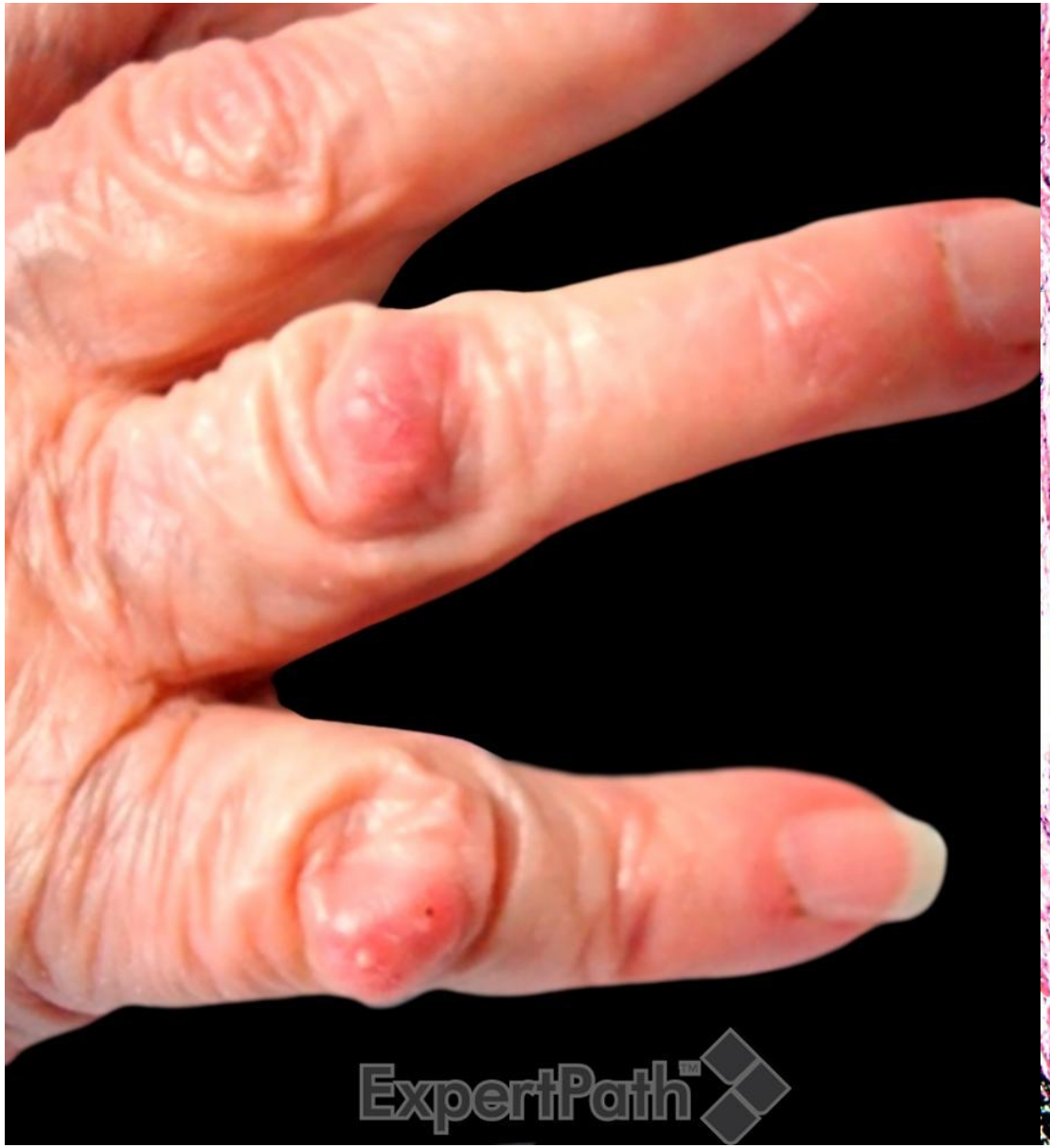
Histopathologic Features:

- Palisaded granulomatous dermatitis, hemorrhage, and eosinophilic fibrinoid necrosis
- May have vasculitic changes

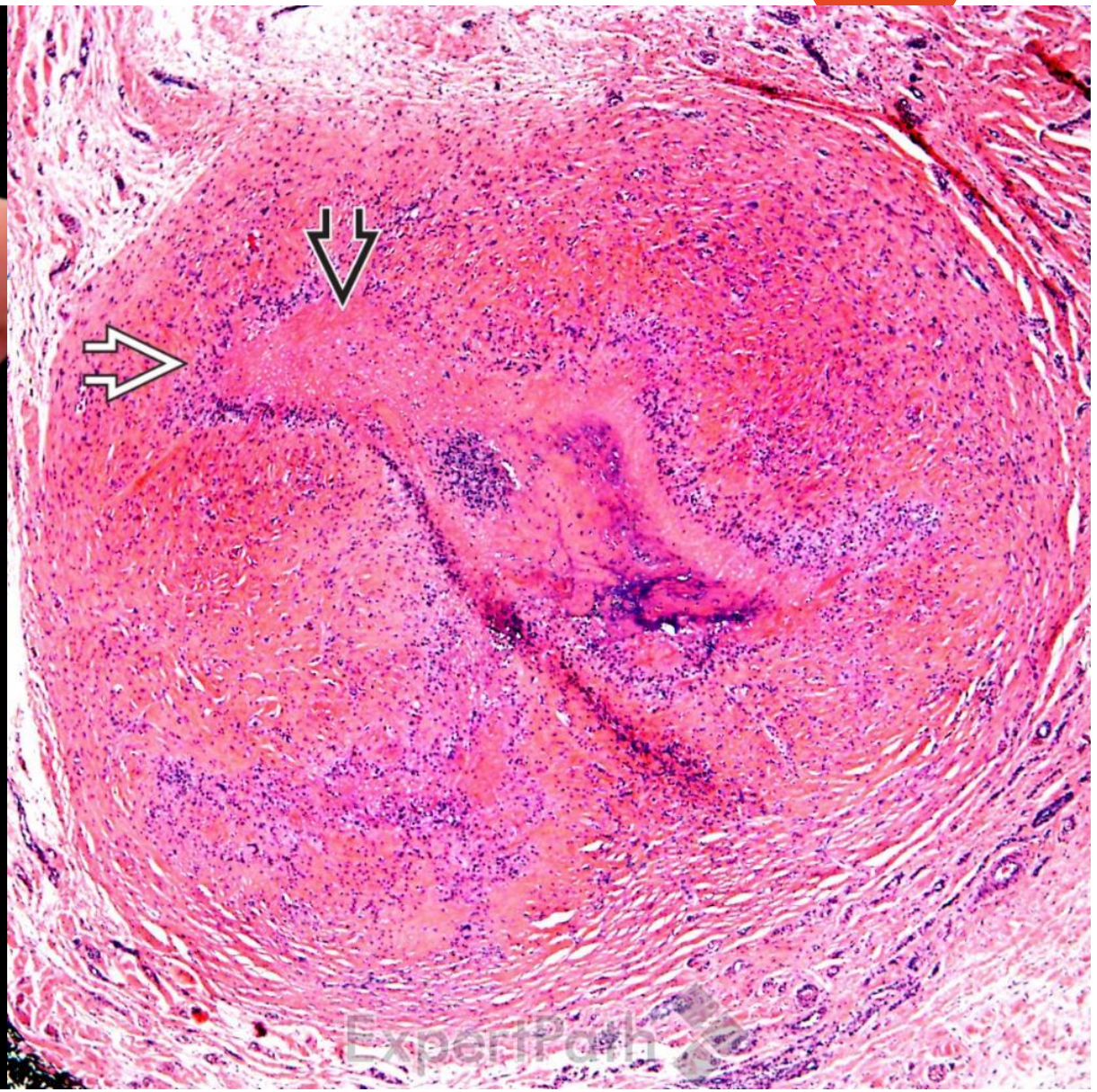
Differential Diagnosis:

- Rheumatic fever nodule, subcutaneous granuloma annulare, and epithelioid sarcoma

Rheumatoid nodule



Firm, pink nodules are shown over the proximal interphalangeal (PIP) joints of the 4th and 5th digits in this woman with rheumatoid arthritis.



Classic appearance of rheumatoid nodule (RN) shows a discrete nodule of fibrous tissue in the subcutis composed of a central area of red necrobiosis (black open arrow) and palisading histiocytes (white open arrow). (Courtesy L. Coleman, MD.)

Necrobiotic Xanthogranuloma

Clinical Features:

- Associated with IgG paraproteinemia, usually kappa subtype
- Indurated papules, nodules, plaques, commonly periorbitally distributed

Histopathologic Features:

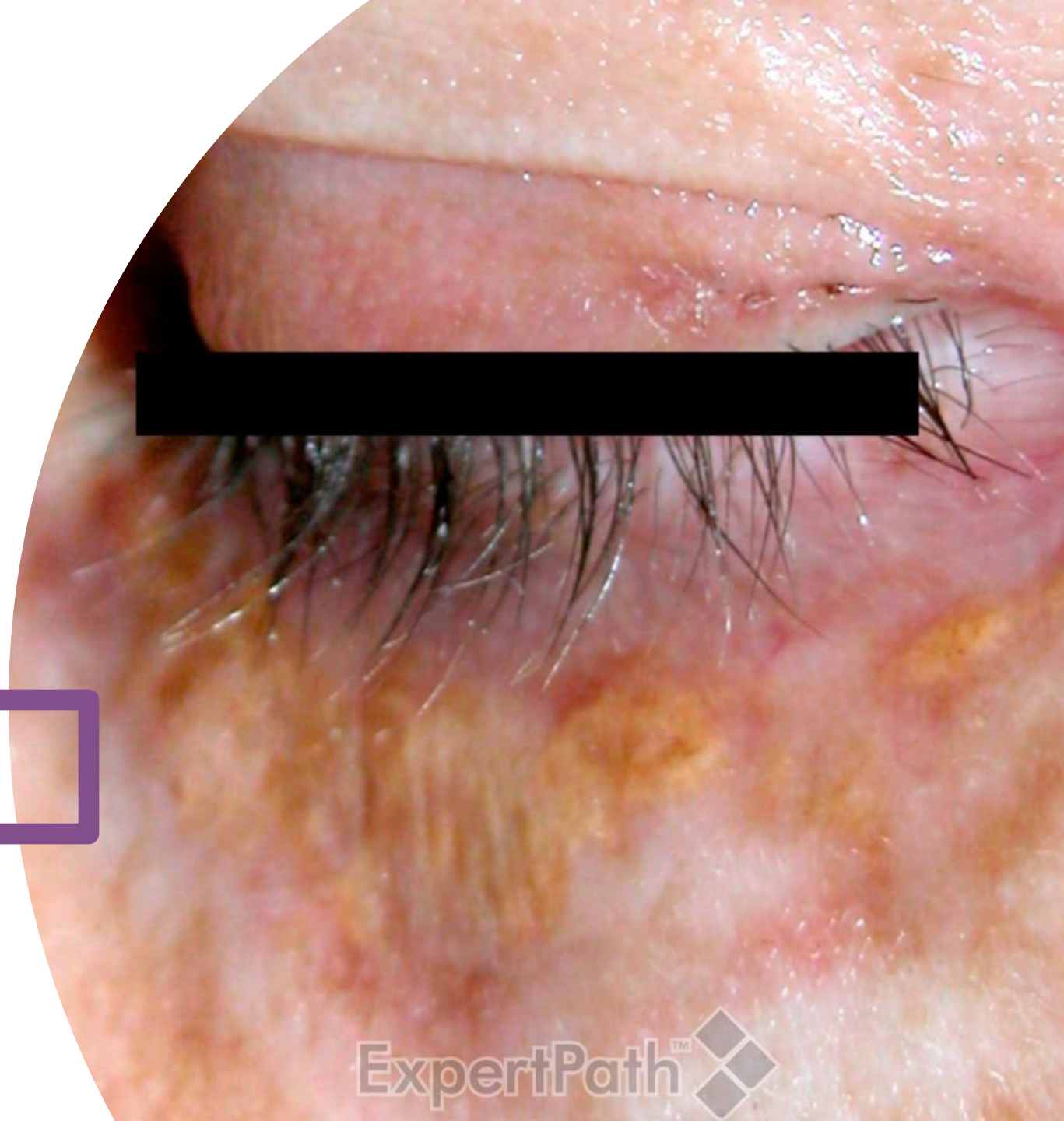
- Broad zones of collagen degeneration, cholesterol clefts, and foreign-body type multinucleated giant cells
- Numerous lymphocytes, plasma cells with lymphoid follicle formation

Differential Diagnosis:

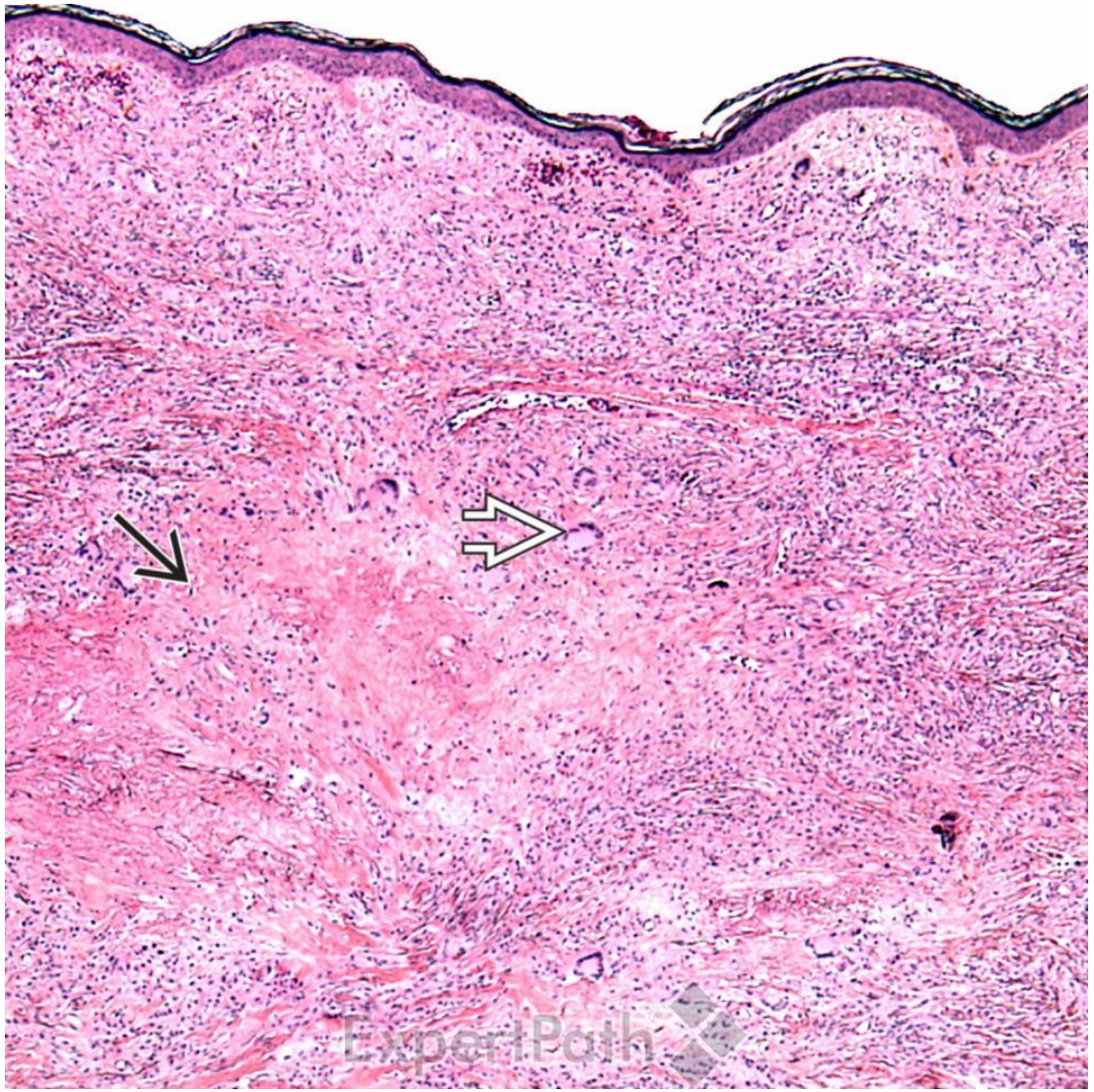
- Xanthoma

Necrobiotic xanthogranuloma

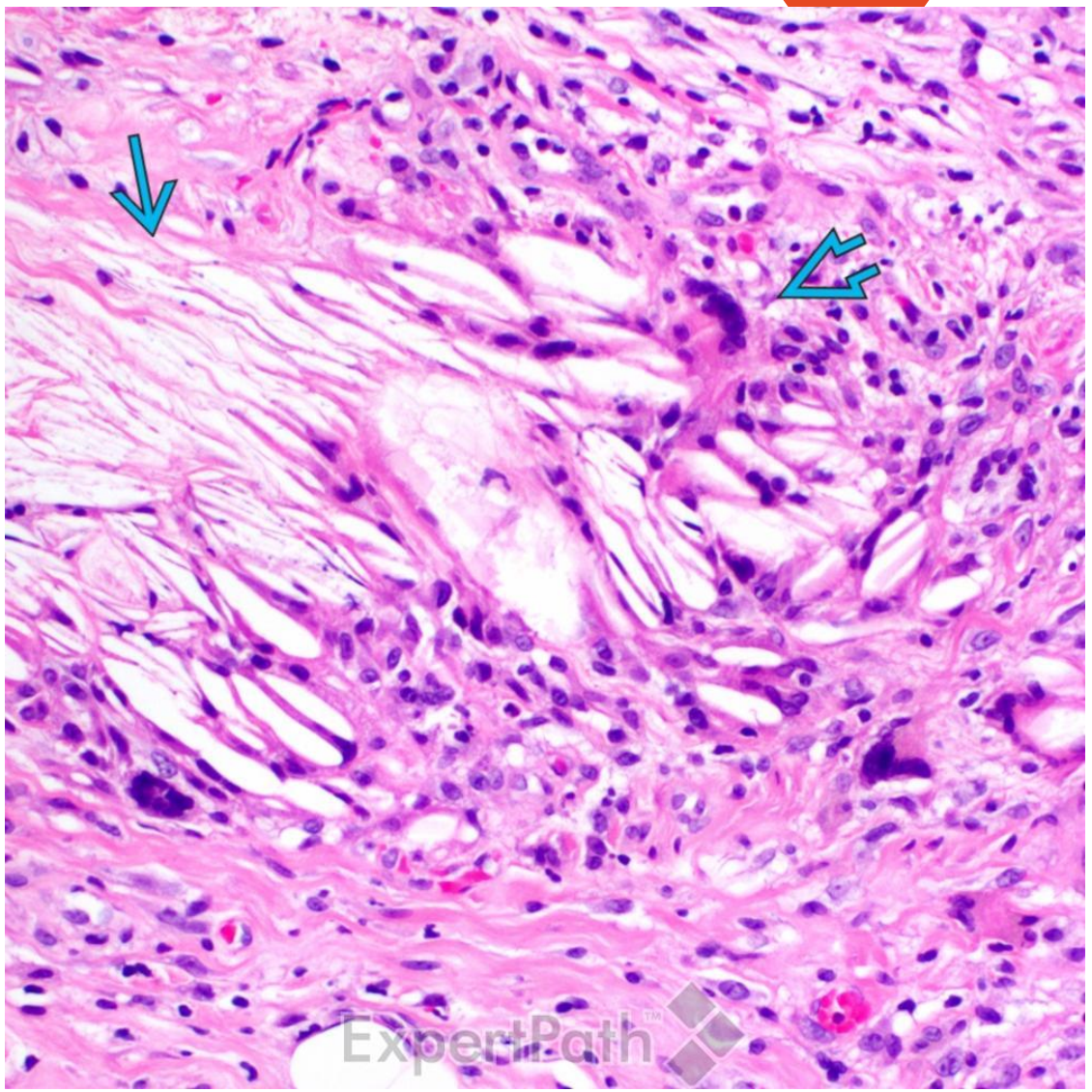
Clinical photo shows yellow-orange papules and plaques on the lower eyelid. Biopsy was compatible with necrobiotic xanthogranuloma.



Necrobiotic xanthogranuloma



In necrobiotic xanthogranuloma, there are broad zones of altered collagen (necrobiosis) (black solid arrow) surrounded by a cellular infiltrate. Giant cells are often prominent (white open arrow).



Multinucleate giant cells (cyan open arrow) surround cholesterol clefts (cyan solid arrow) in the dermis in necrobiotic xanthogranuloma.

Summary of Palisading Granulomas

Disease	Area of necrobiosis	Degree of collagen alteration	Mucin deposition	Lipid in dermis	Vascular changes
Granuloma annulare	Upper to mid dermis	Focal	Common	Rare	Rare
Necrobiosis lipoidica	Reticular dermis	Confluent	Rare	Common	Endothelial cell hypertrophy and fraction
Rheumatoid nodule	Reticular dermis/ subcutis	Confluent	Variable	Variable	Variable
Rheumatic fever nodule	Subcutis	Confluent	Variable	Variable	Vessel perforation
Subcutaneous granuloma annulare	Reticular dermis/ subcutis	Confluent	Comment	Variable	Variable

Palisaded Neutrophilic and Granulomatous Dermatitis

Clinical Features

Associated Systemic Diseases:

- Systemic Lupus Erythematosus
- Rheumatoid Arthritis
- Sjogren Syndrome
- Waggoner Granulomatosis (ANCA positive vasculitides)
- Inflammatory Bowel Disease
- Hepatitis
- Lymphoproliferative Disease
- Myelodysplastic Syndromes
- Cancer
- Thyroid Disease
- Diabetes Mellitus
- Drug Reactions
- Infections

Skin Presentation:

- Skin-colored to erythematous papules with crust, ulceration, or umbilication
- Predominantly located on extremities and trunk
- Often symmetrically distributed

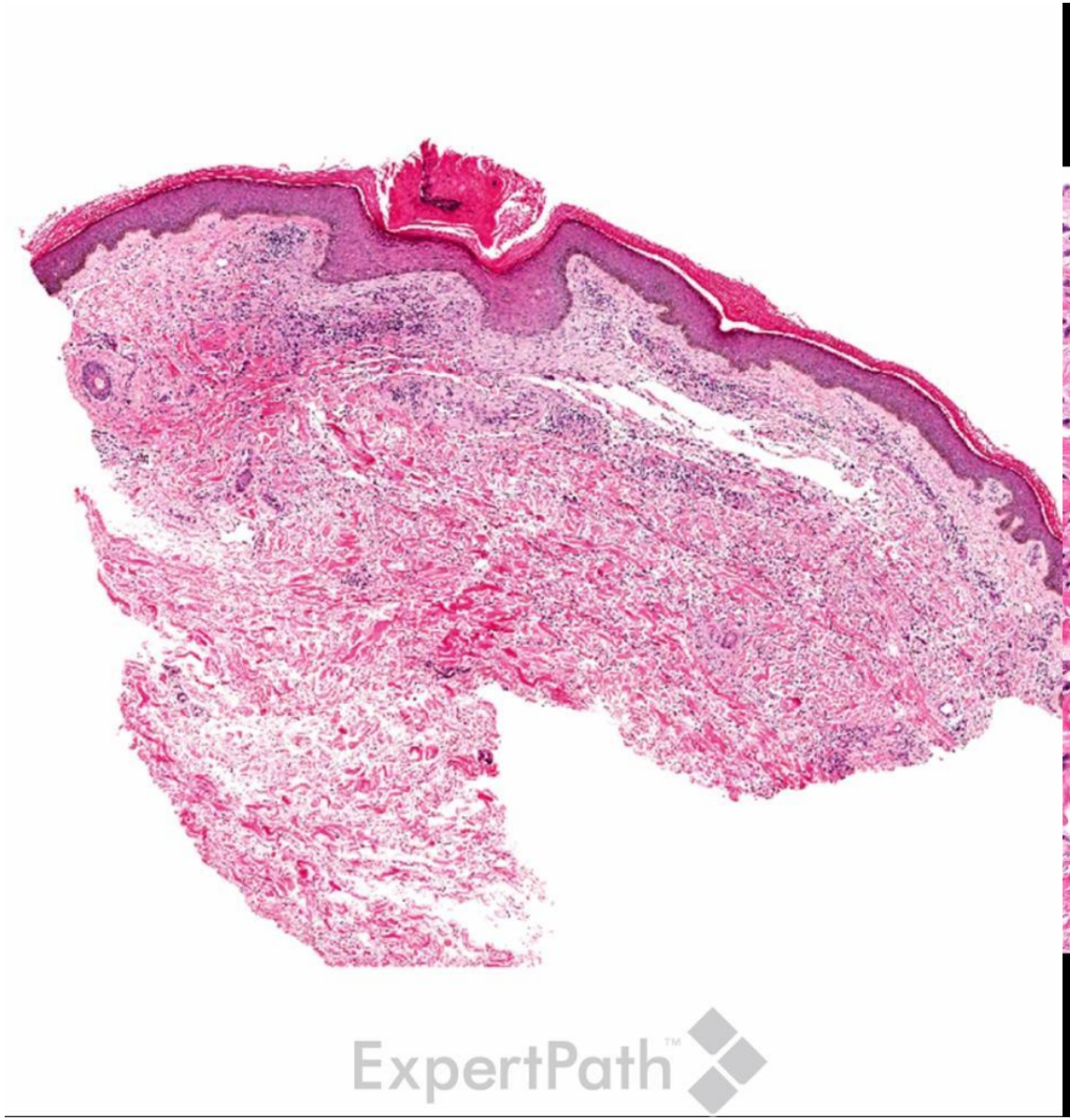
Histopathologic Features

- Variable histology due to different stages of development
- **Early Lesions:**
  - Collagen degeneration
  - Infiltrate of neutrophils
  - Nuclear debris
  - Focal leukocytoclastic vasculitis
- **Fully Developed Lesions:**
  - Resemble Granuloma Annulare
  - Palisaded and granulomatous dermatitis
  - Surrounding zones of fibrin deposition and necrosis
  - Central area containing mucin

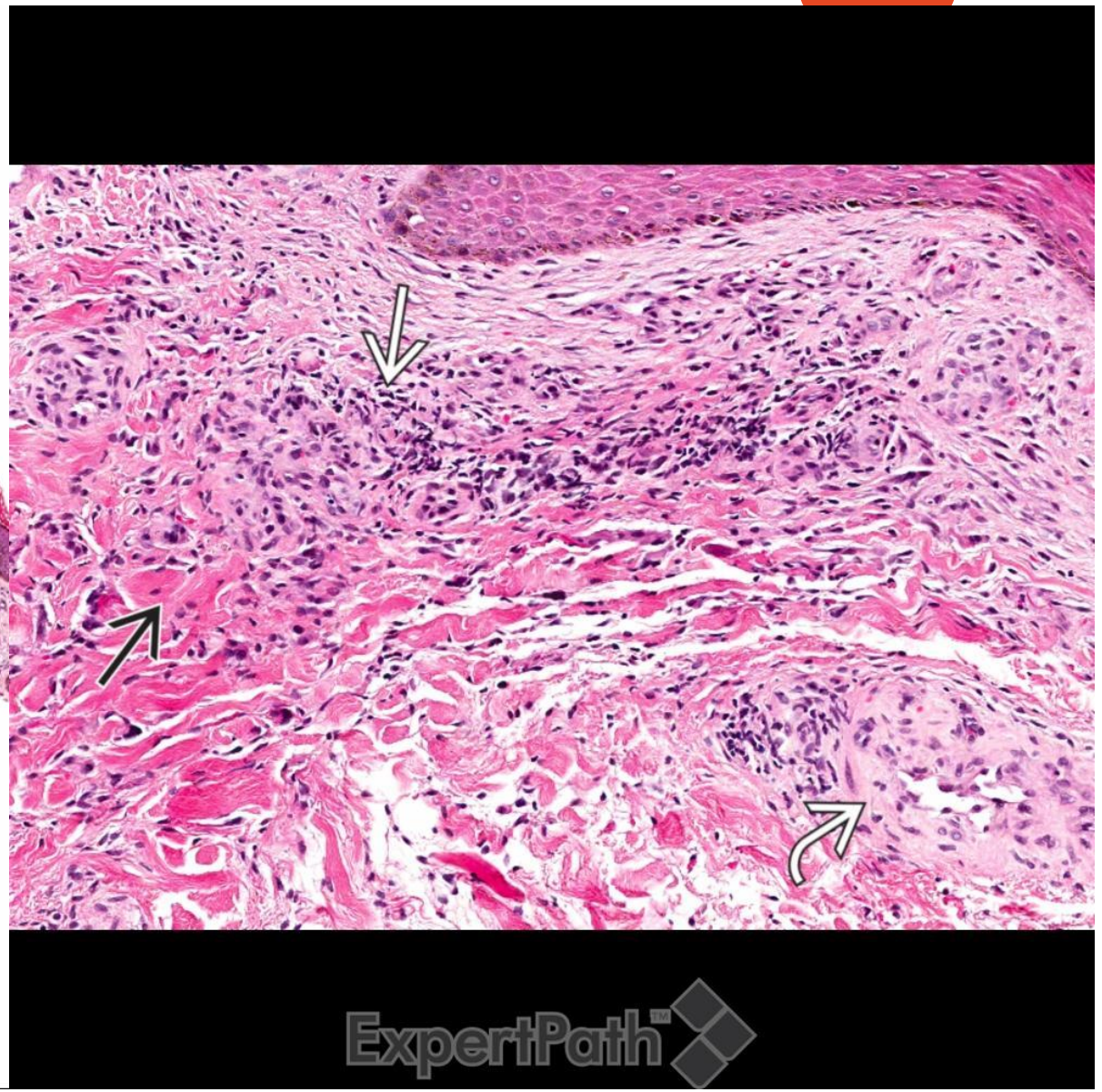
Differential Diagnosis

- Granuloma Annulare
- Necrobiosis Lipoidica
- Rheumatoid or Rheumatic Fever Nodules

Palisaded Neutrophilic and Granulomatous Dermatitis



Low-power view reveals a perivascular and interstitial pattern that imparts a busy look to the dermis.



Altered collagen (black solid arrow), endothelial swelling (white curved arrow), and interstitial inflammation (white solid arrow) are seen in this example of PNGD.

Infectious Palisaded Granulomatous Dermatitis

Response to infections caused by:

- Typical and atypical Mycobacteria
- Phaeohyphomycosis
- Syphilis
- Sporotrichosis
- Cryptococcosis
- Coccidioidomycosis
- Cat Scratch Disease
- Lymphogranuloma Venereum
- Schistosomiasis

Histologic Features

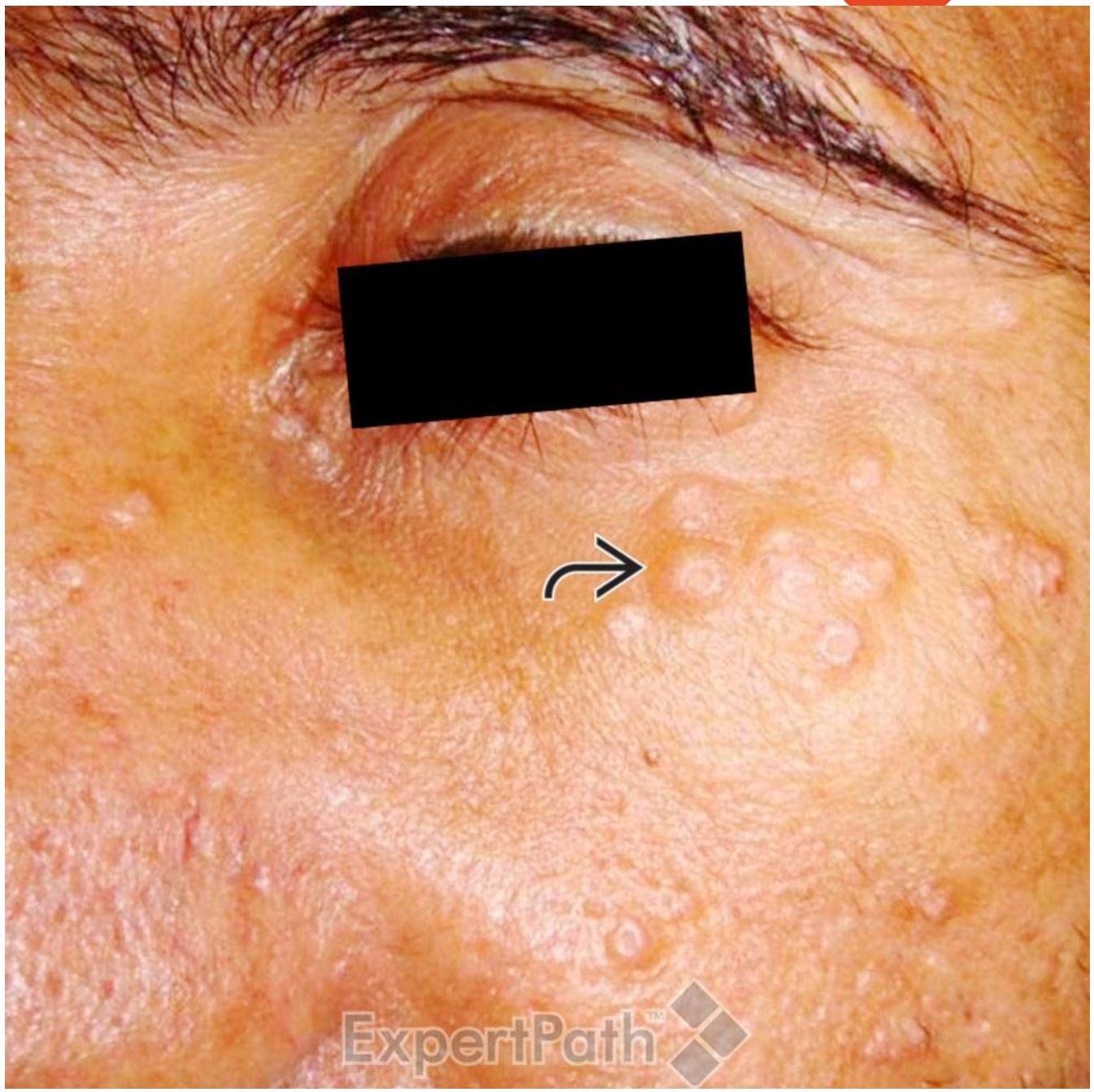
- Palisaded granulomatous dermatitis
- Central necrosis without much mucin
- Numerous neutrophils

Differential Diagnosis

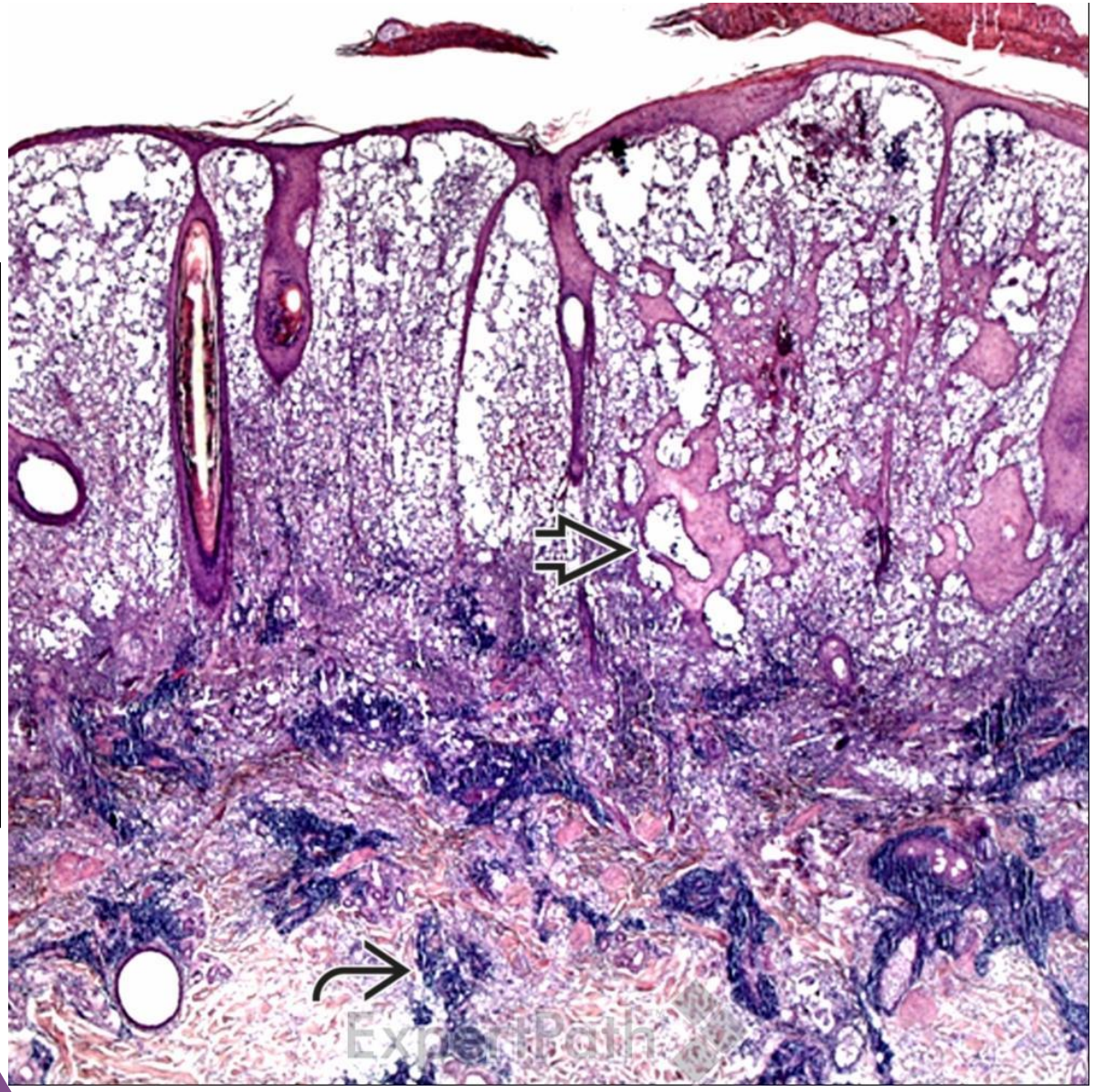
- Neutrophils and neutrophilic debris in association with palisades of granulomas
- Rheumatoid nodule
- Rheumatic fever nodule
- Palisaded neutrophilic and granulomatous dermatitis
- Ruptured follicles and follicular cysts/sinuses

Cryptococcosis

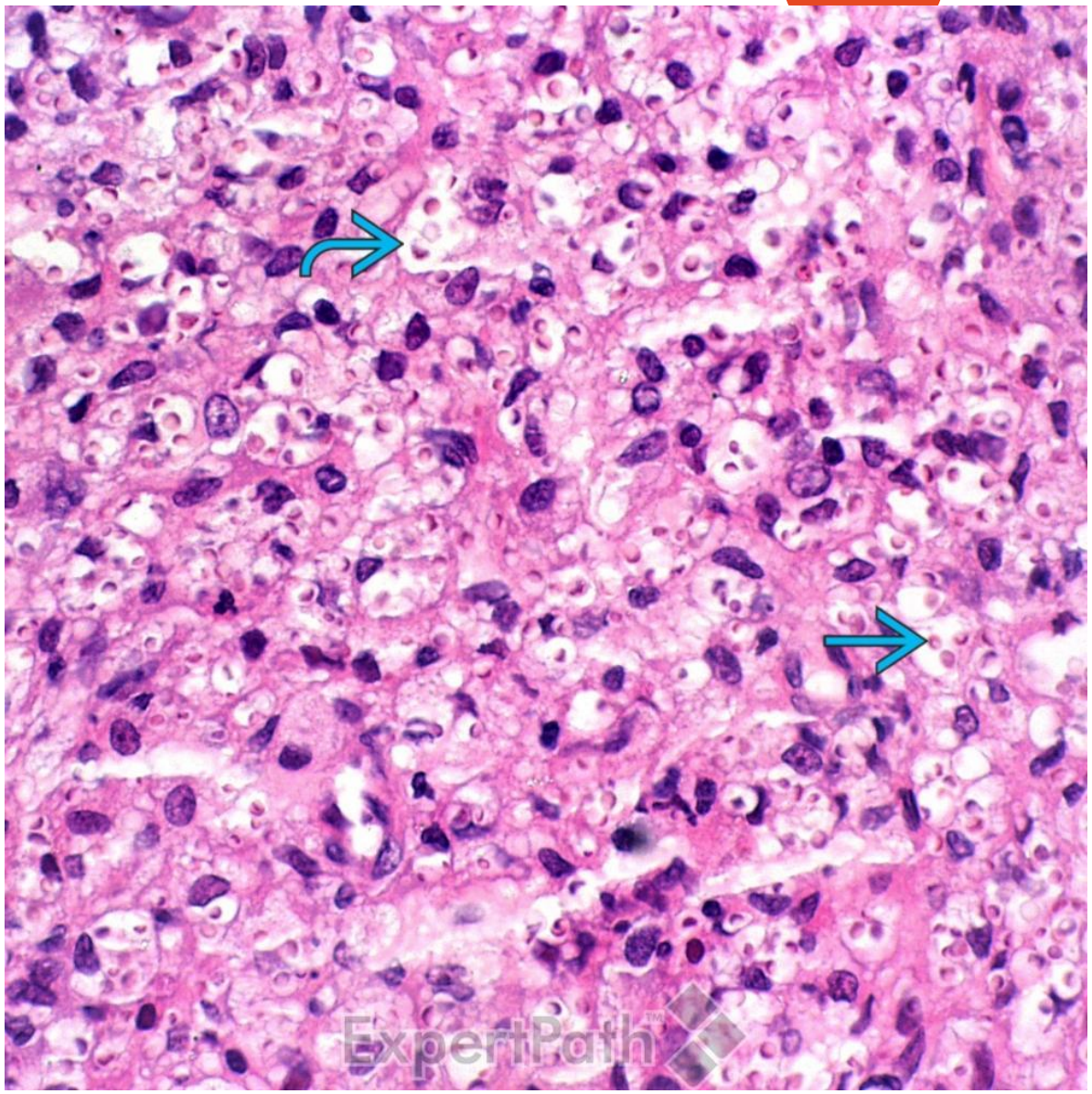
Cutaneous cryptococcosis (CC) appears most often in immunosuppressed patients, such as this HIV patient who presented with disseminated disease and molluscum-like umbilicated papules (black curved arrow). (Courtesy C. Ramos, MD.)



cryptococcosis



Low-power view of CC demonstrates pseudoepitheliomatous hyperplasia (black open arrow) as well as abundant dermal inflammation and dermal granulomatous inflammation (black curved arrow).



High-power view of CC demonstrates numerous yeast-like fungi (cyan solid arrow) with a surrounding clear halo (cyan curved arrow) indicative of cryptococcosis. (Courtesy S. Billings, MD.)

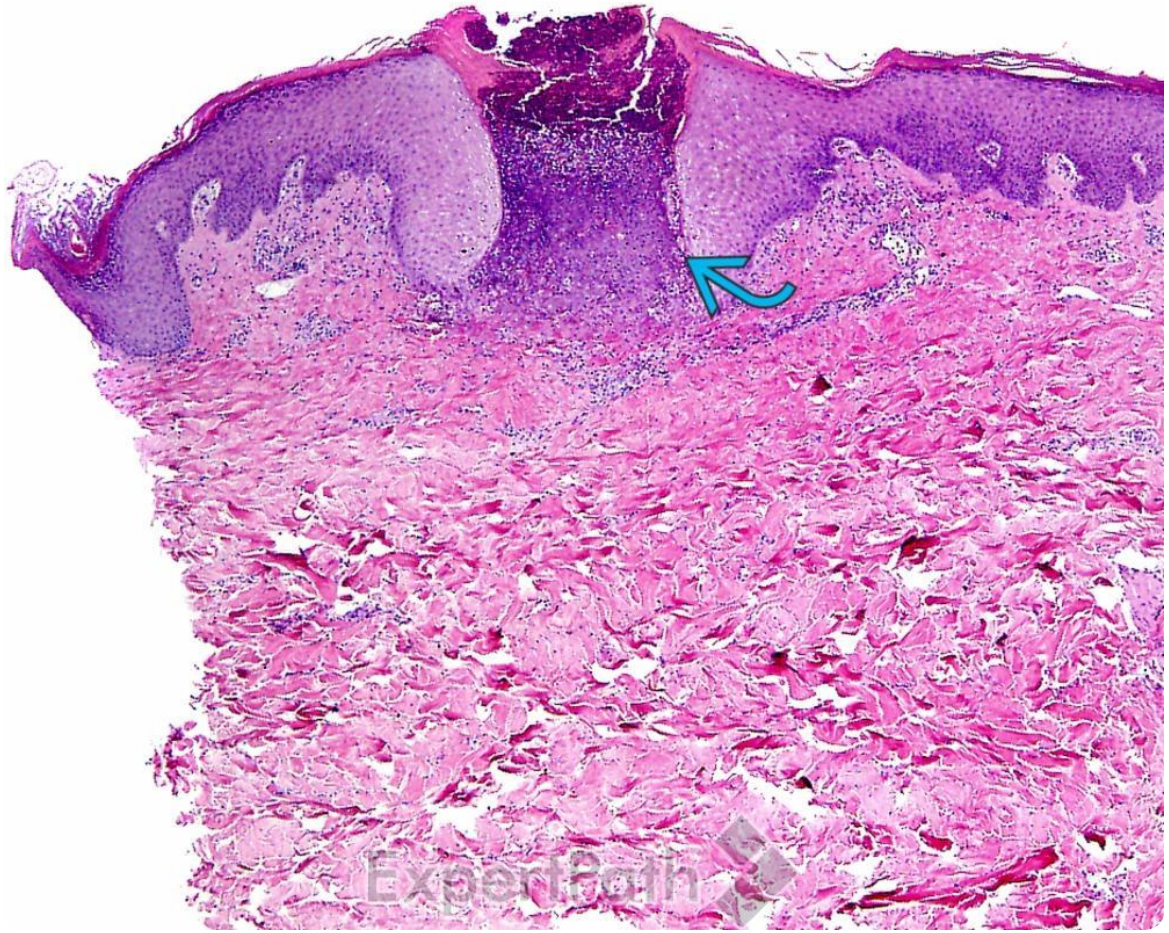
Perforating Dermatoses

What is a perforating disorder?

Four Primary Perforating Dermatoses:

These may represent different stages or regional developments in association with renal disease and diabetes mellitus.

- Kyrle Disease
- Perforating Folliculitis
- Reactive Perforating Collagenosis
- Elastosis Perforans Serpiginosa



Low-power view of a perforating disorder demonstrates transepidermal elimination of collagen through a central plug (cyan curved arrow).

Acquired Perforating Dermatosis

Clinical Features:

Onset occurs at any age.

Few to many lesions appear, often on the extensor surfaces.

Commonly associated with chronic renal failure and diabetes mellitus.

Lesions are pruritic, appear as non-confluent follicular or extra-follicular papules.

Central conical keratotic plug observed.

Differential Diagnosis:

Elastosis Perforans Serpiginosa

Acneiform eruptions

Keratosis Pilaris

Histopathologic Features:

Keratotic plug with epidermal invagination over the perforation.

Perforation occurs in the follicular lesion through the infundibulum.

Bordered by acanthotic, hyperkeratotic epidermis.

Inflammatory debris found in the channel with basophilic collagen or eosinophilic elastin.

Bright eosinophilic elastic fibers seen within basophilic collagenous debris in the transepidermal channel.

Granulomatous reaction at the base.

Elastosis Perforans Serpiginosa

Clinical Features:

Presents as solitary or few lesions on the nape of the neck.

Associated with Down syndrome and connective tissue disorders.

Arcuate lesions formed by coalescence of keratotic papules with central plugs.

Differential Diagnosis:

Acquired Perforating Dermatosis

Perforating Folliculitis

Reactive Perforating Collagenosis

Histopathologic Features:

Increased number and size of elastin fibers at the base.

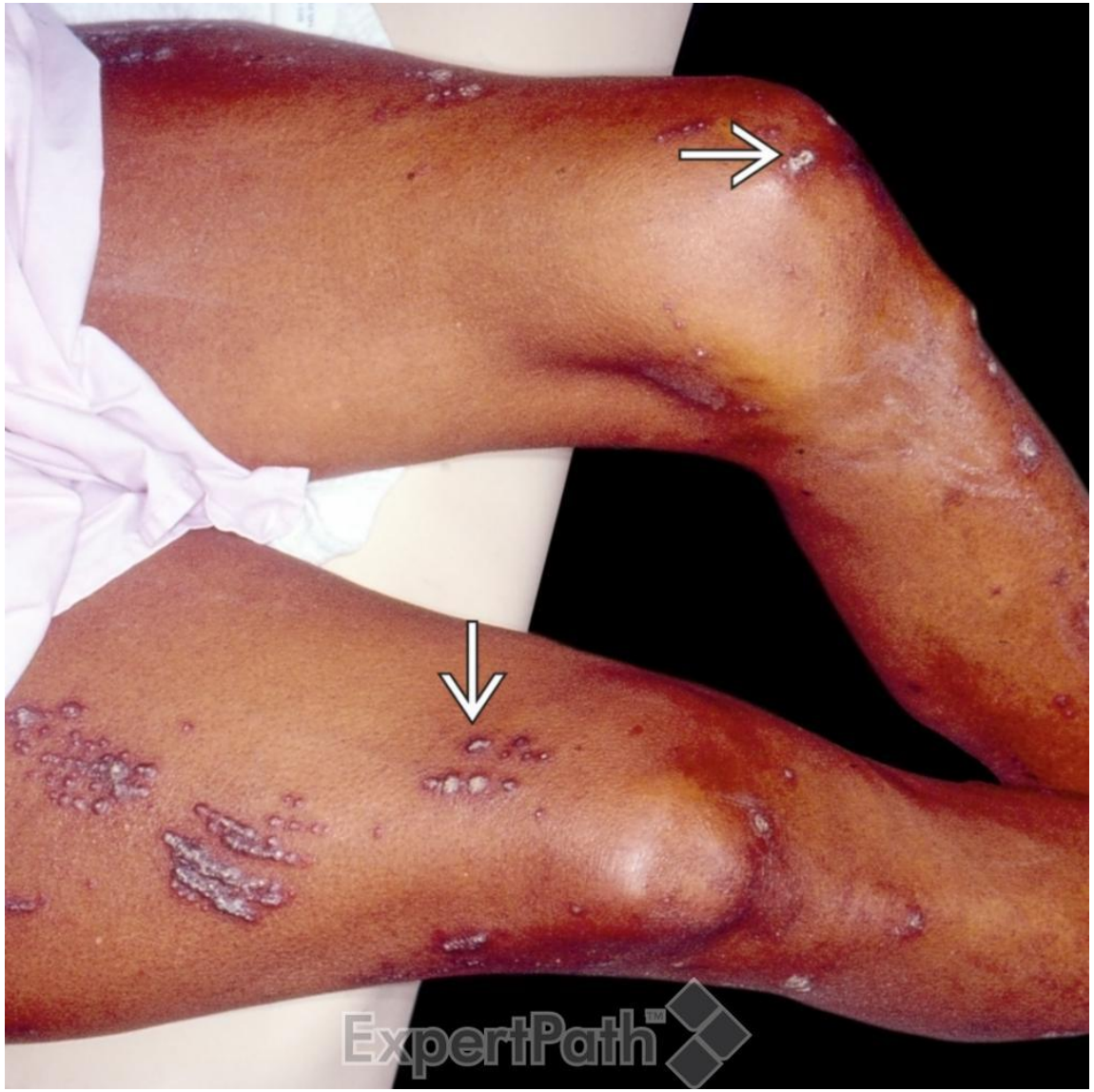
Narrow transepidermal channel delimited by acanthotic, hyperkeratotic epidermis.

Wedge-shaped parakeratotic plug containing aggregates of neutrophilic debris.

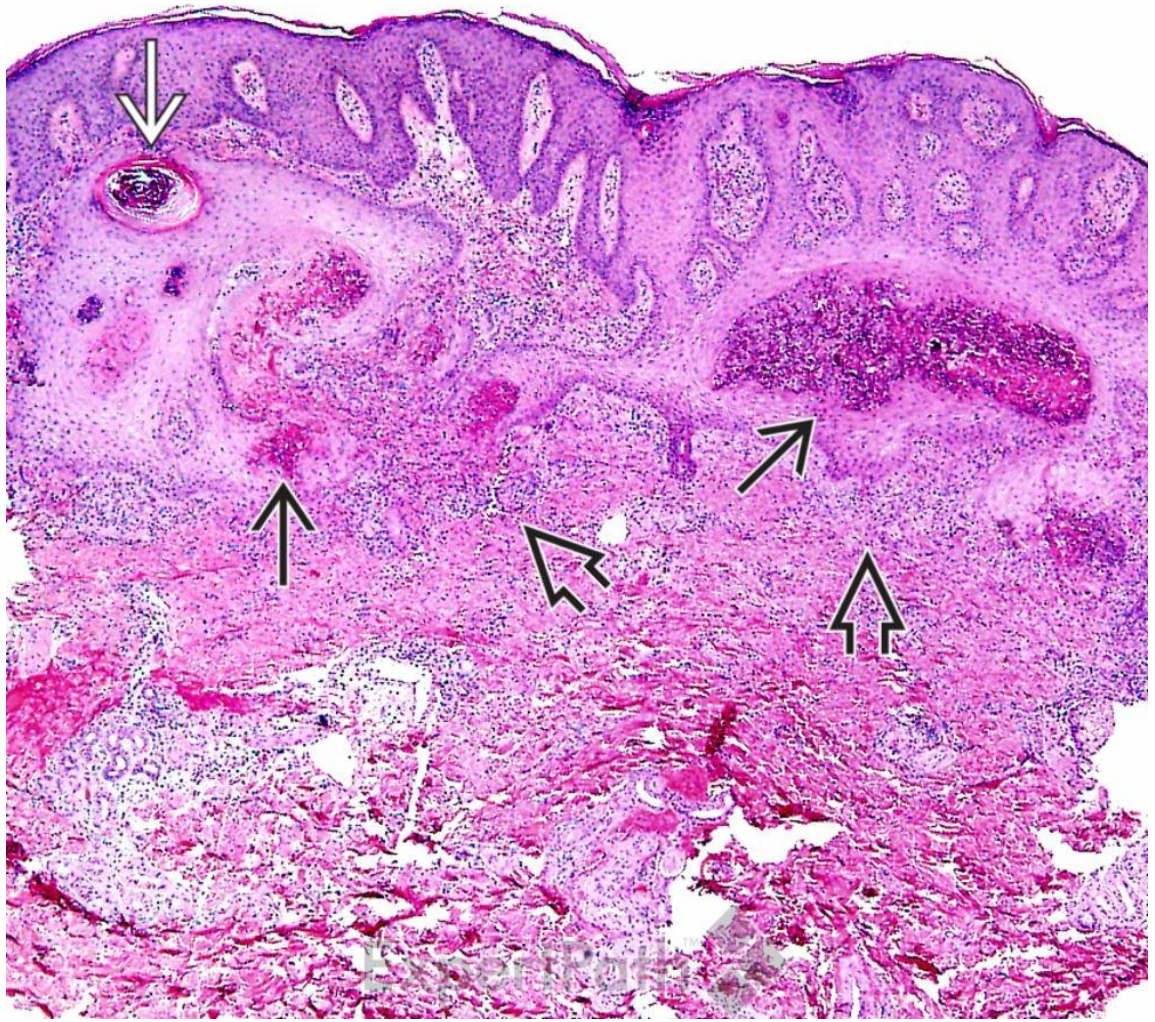
Bright eosinophilic elastin among basophilic debris in the channel.

Granulomatous reaction at the base.

Perforating folliculitis

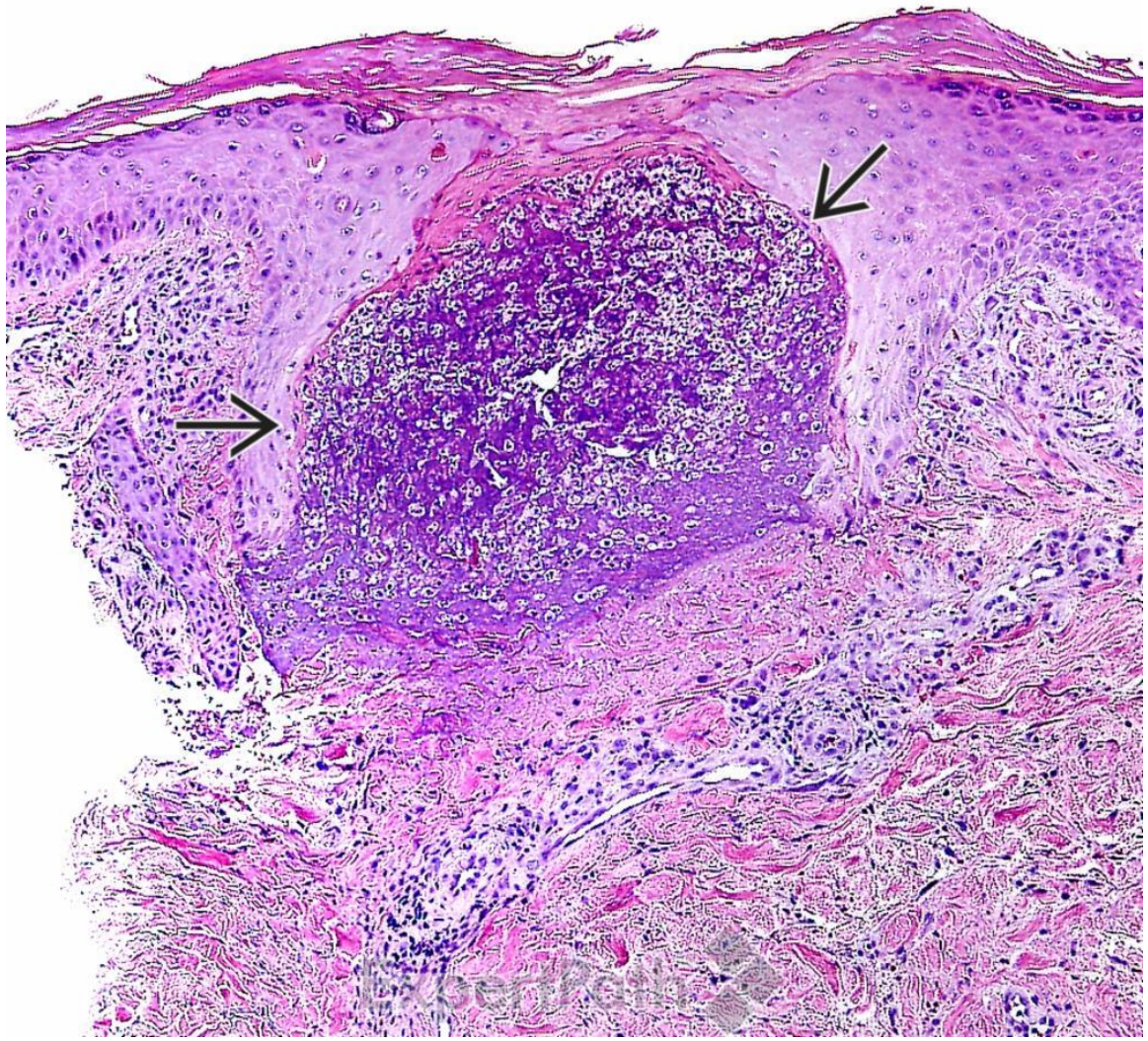


Clinical photo of a renal transplant patient with perforating folliculitis shows nodules with a central keratotic center (white solid arrow) and koebnerization over the anterior thighs.



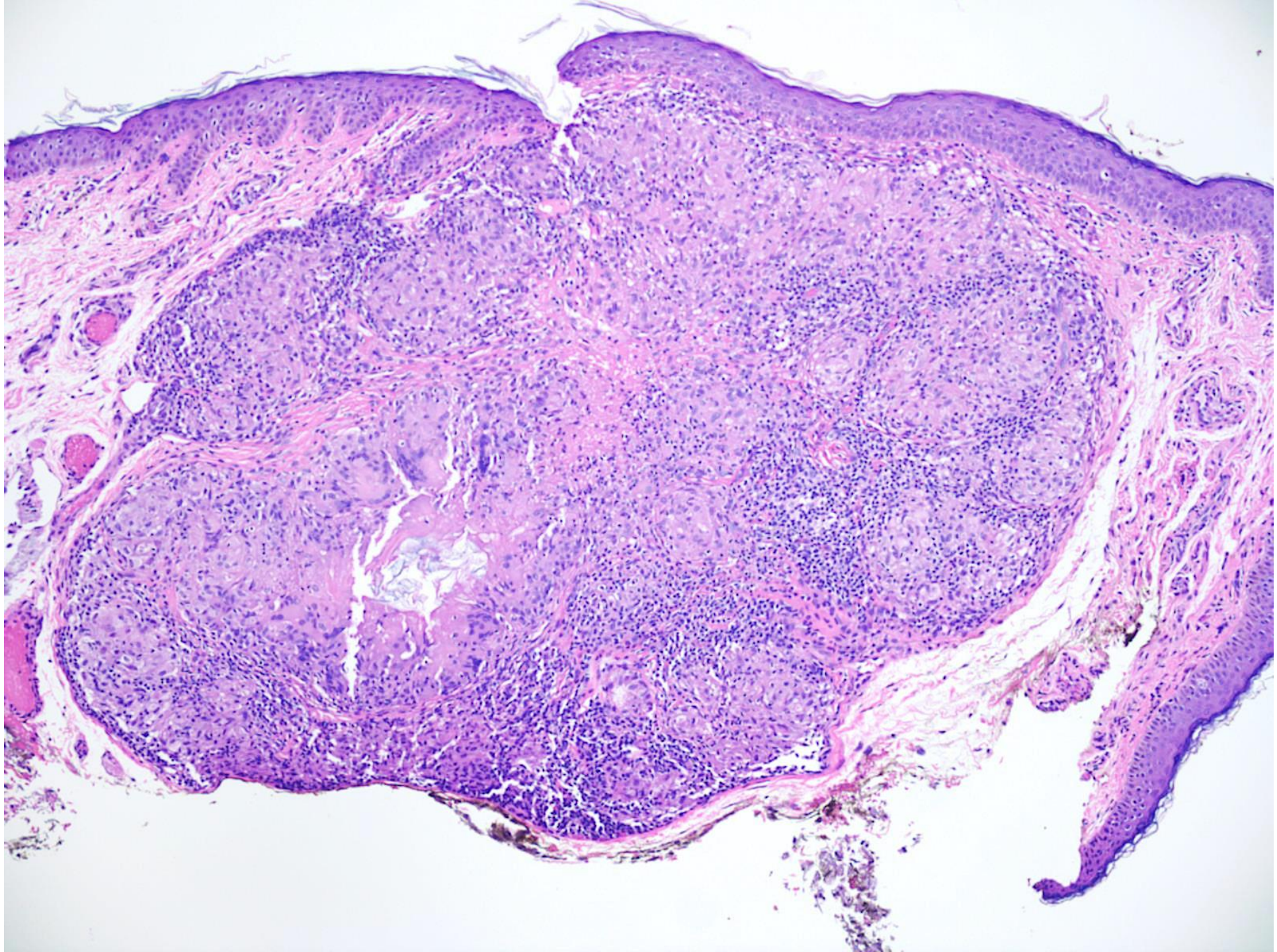
Perforating folliculitis shows degenerated collagen fibers (black solid arrow) perforating through and extending into the hair follicle (white solid arrow) epithelium with surrounding inflammation (black open arrow). (Courtesy R. Harris, MD.)

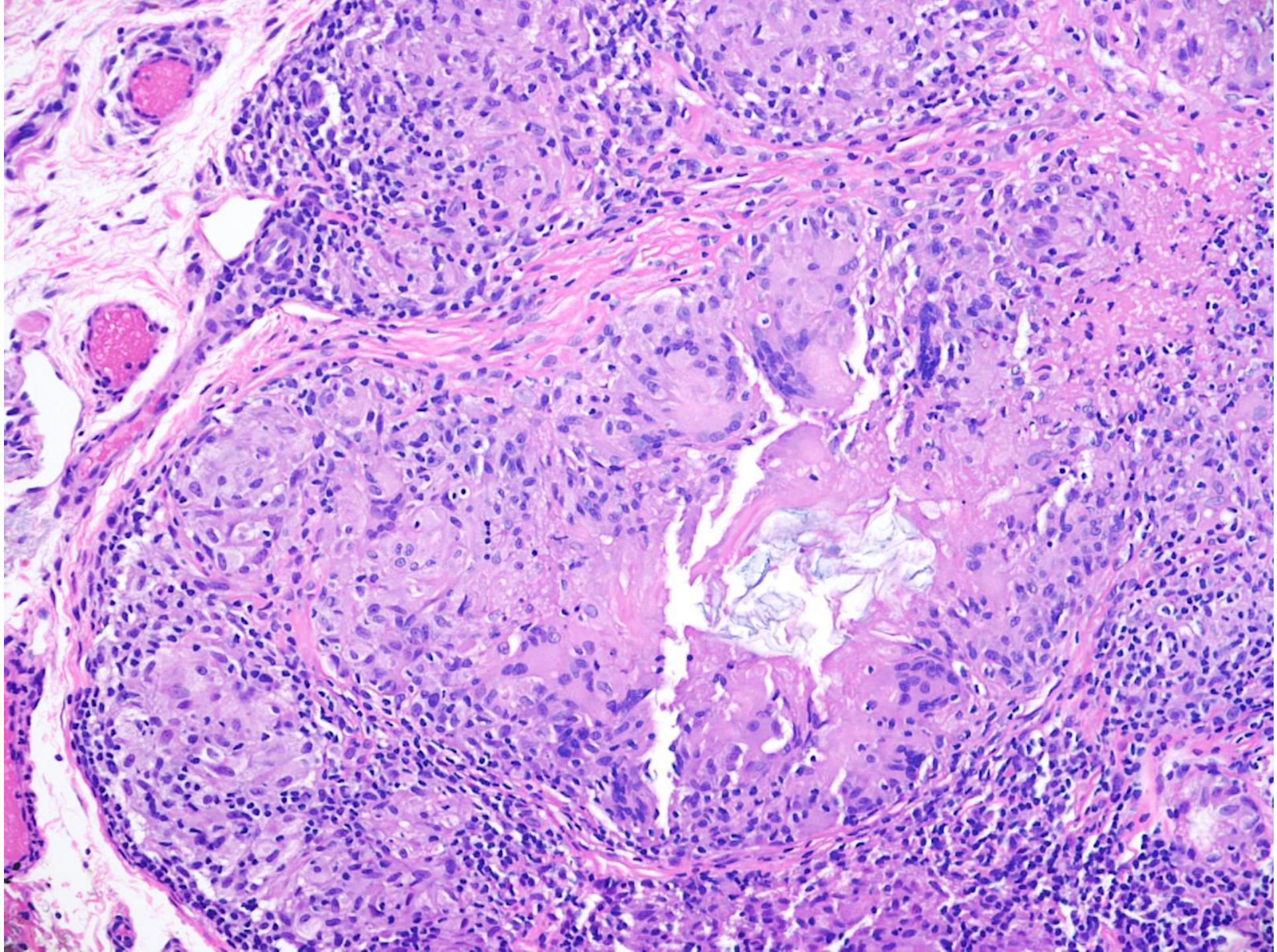
Perforating disorder

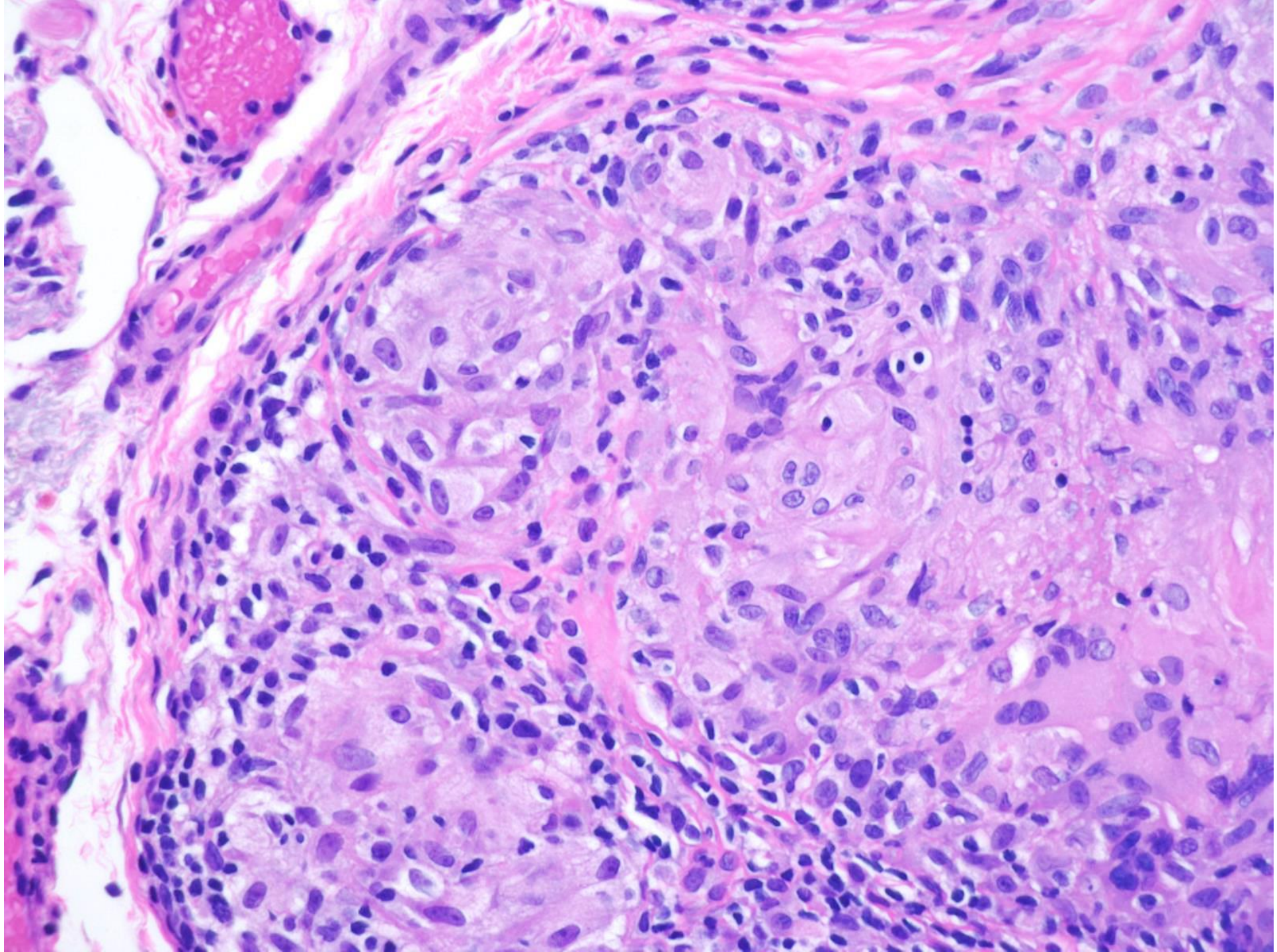


Perforating disorder shows a cup-shaped invagination of amorphous material (black solid arrow) being transepidermally eliminated. Elastin stain, collagen stain, and clinical history would help determine etiology. (Courtesy K. Duffy, MD.)

Quiz cases







Q1. 58F (Indian), numerous 1-3 mm skin-colored papules, periorbitally distributed; r/o Syringoma, molluscum, and trichoepithelioma

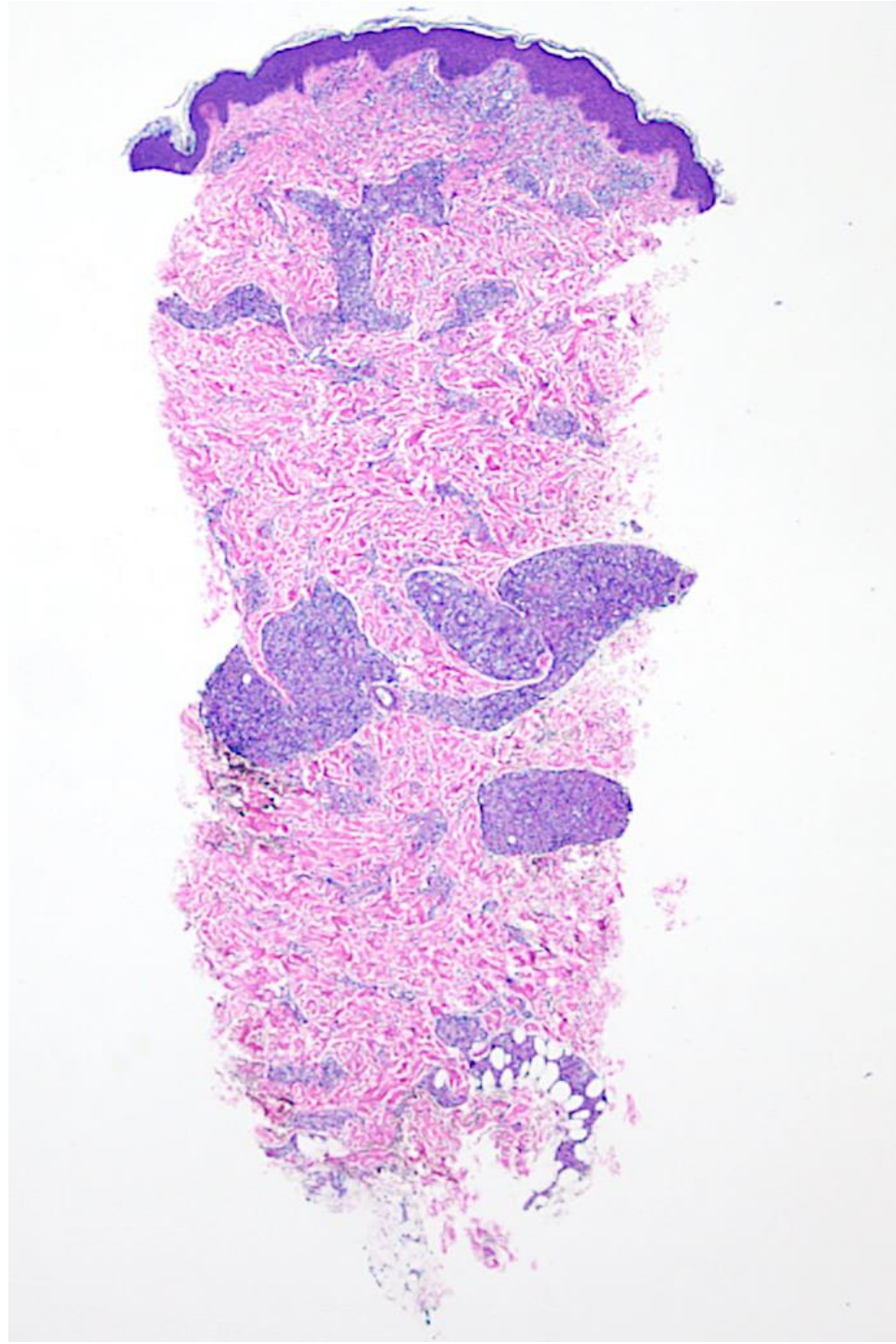
A. Lepromatous leprosy

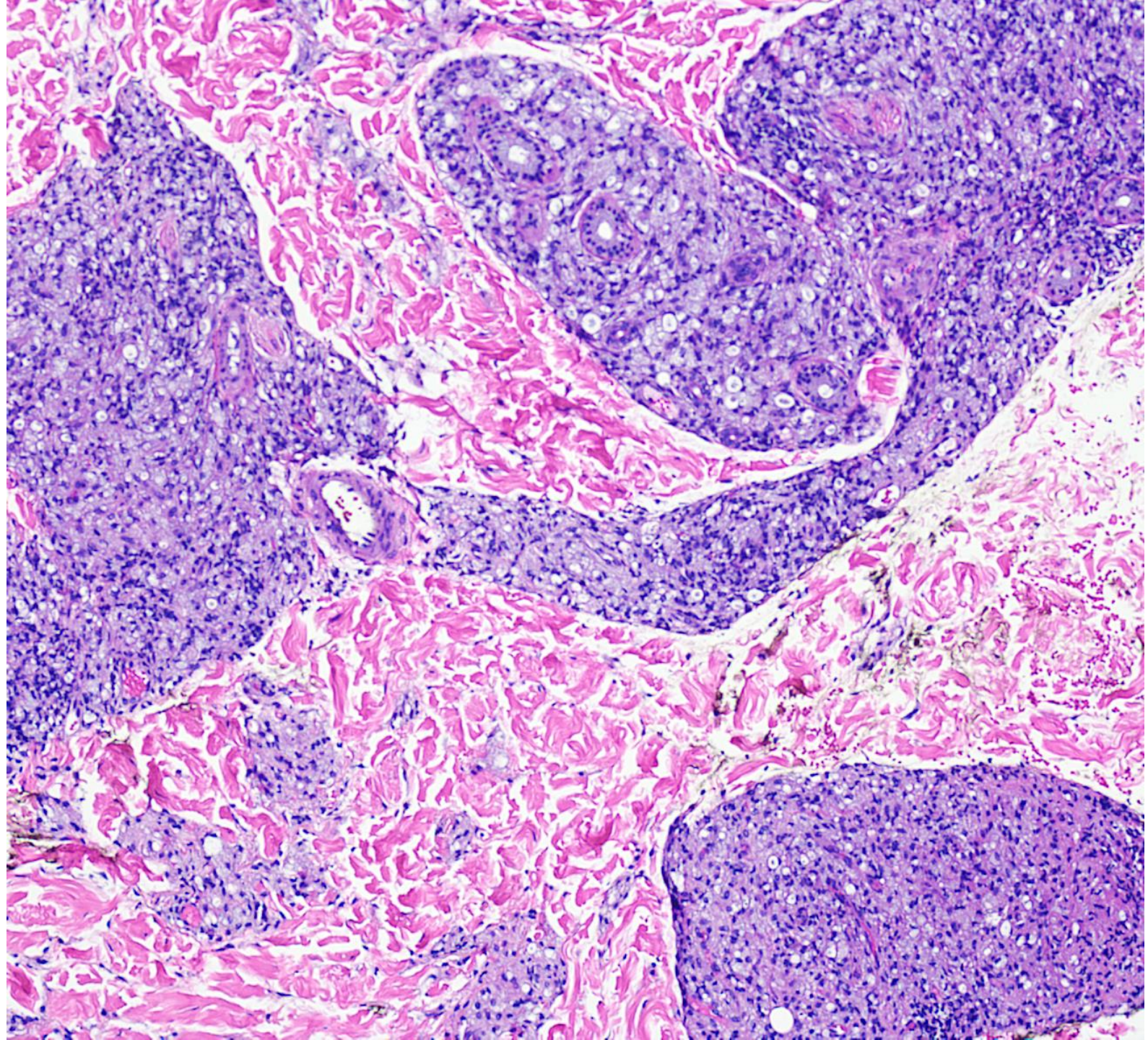
B. Foreign body granuloma and reaction

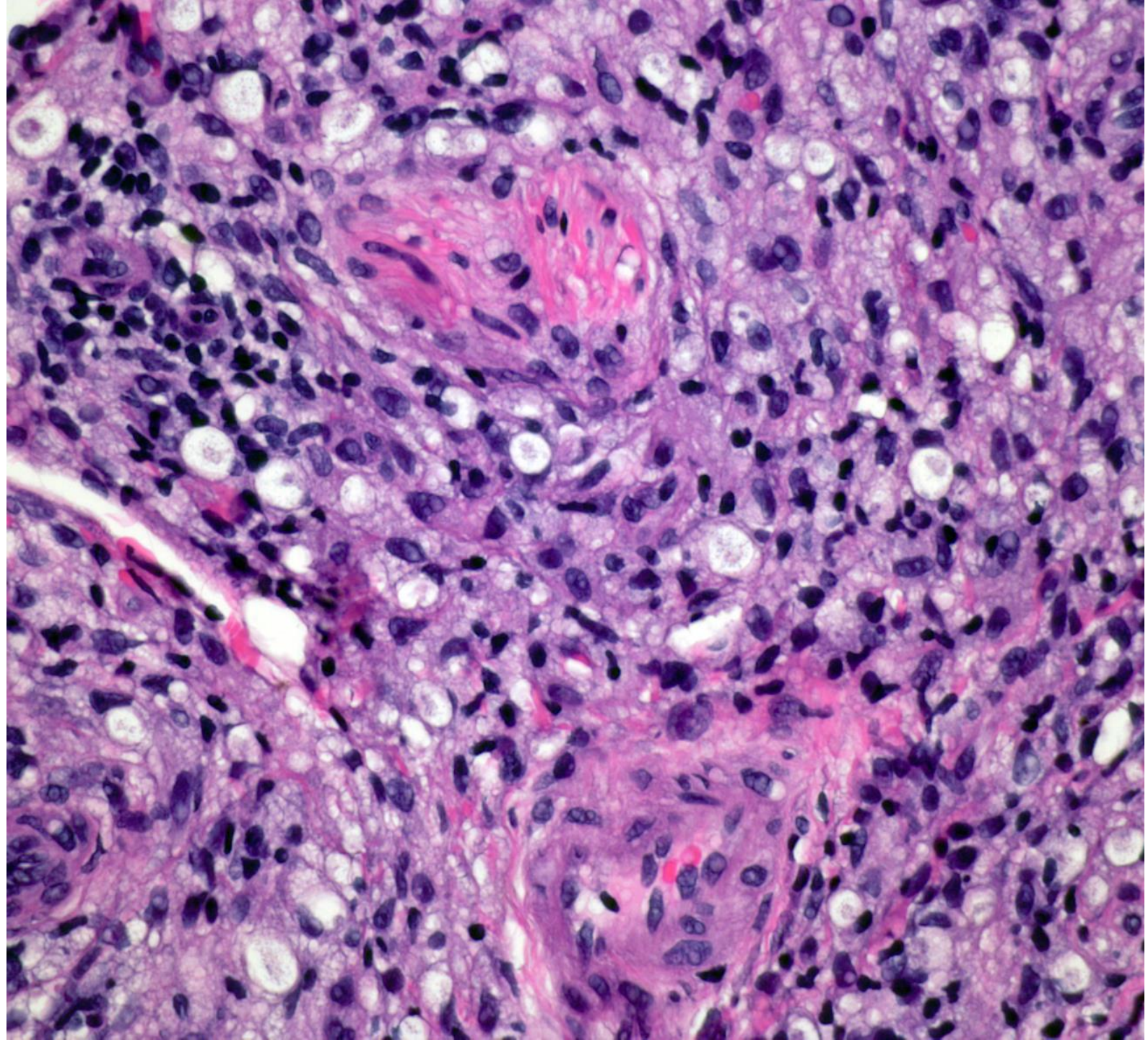
C. Tuberculosis

D. Granuloma annulare

E. Sarcoidosis vs. acne rosacea







Q2. 18F (Indian), nodules on the forehead, facial cheeks, and trunk; r/o acne vulgaris, sarcoidosis

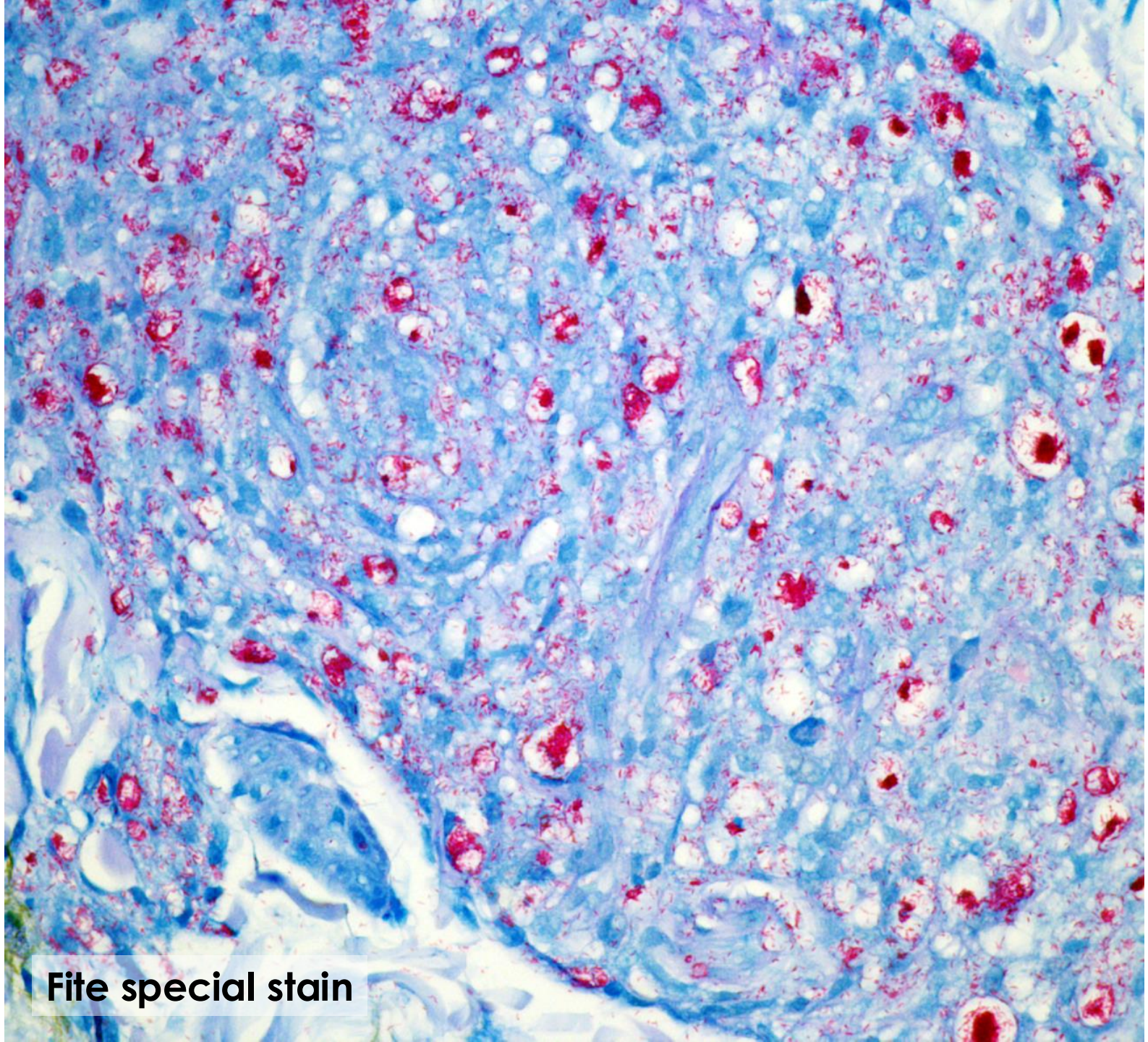
A. Sarcoidosis vs. acne rosacea

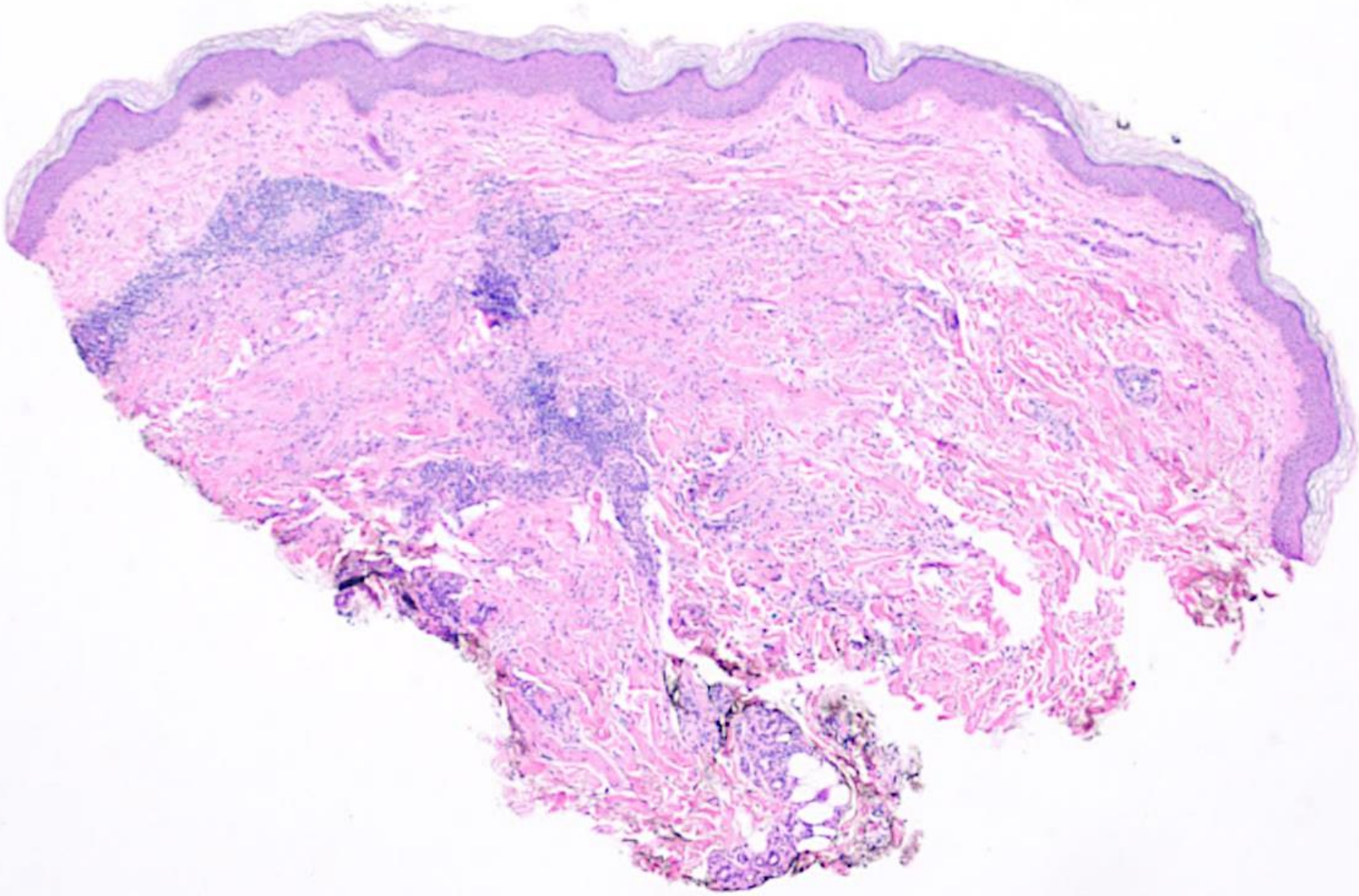
B. Foreign body granuloma and reaction

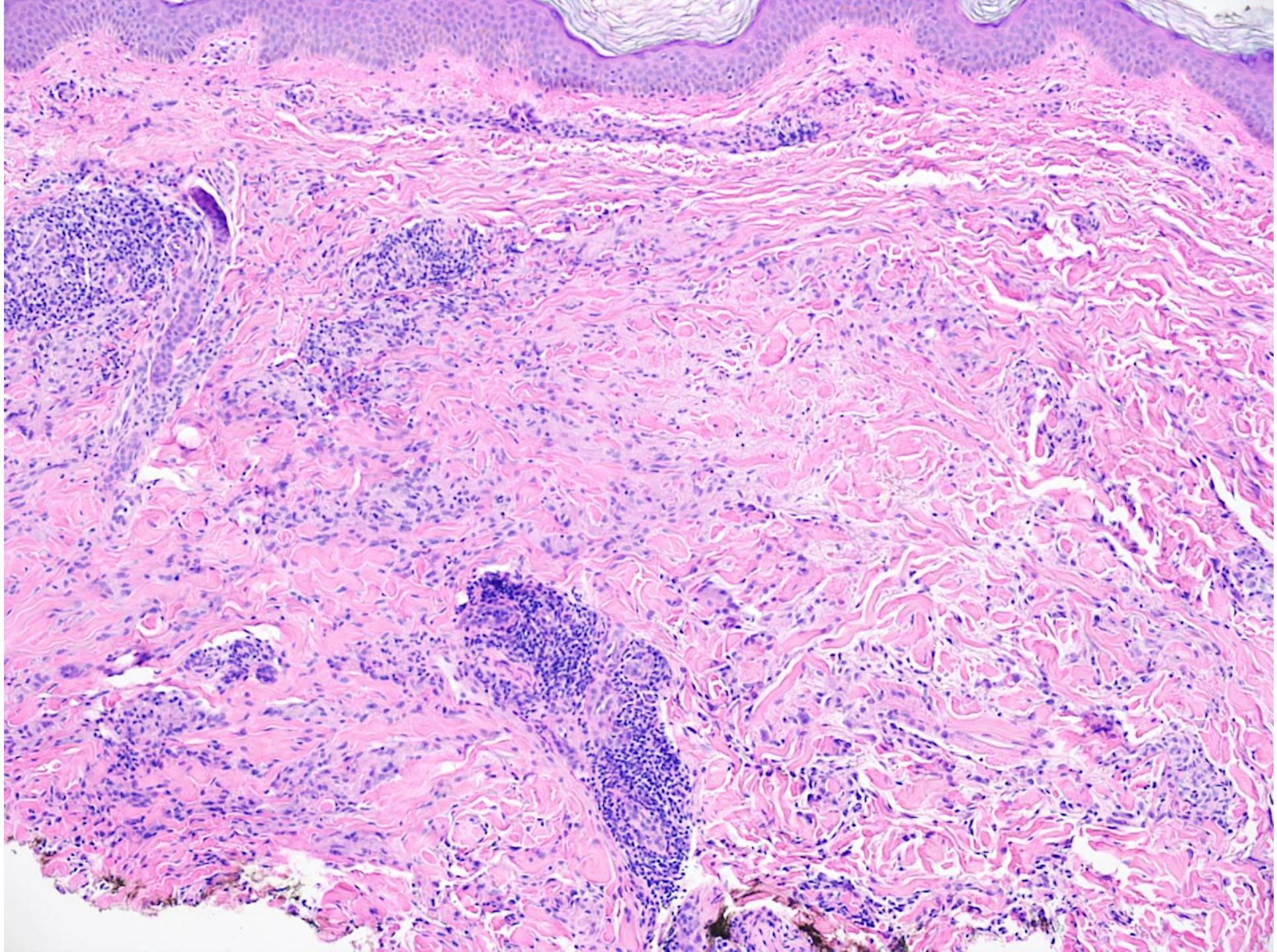
C. Lepromatous leprosy

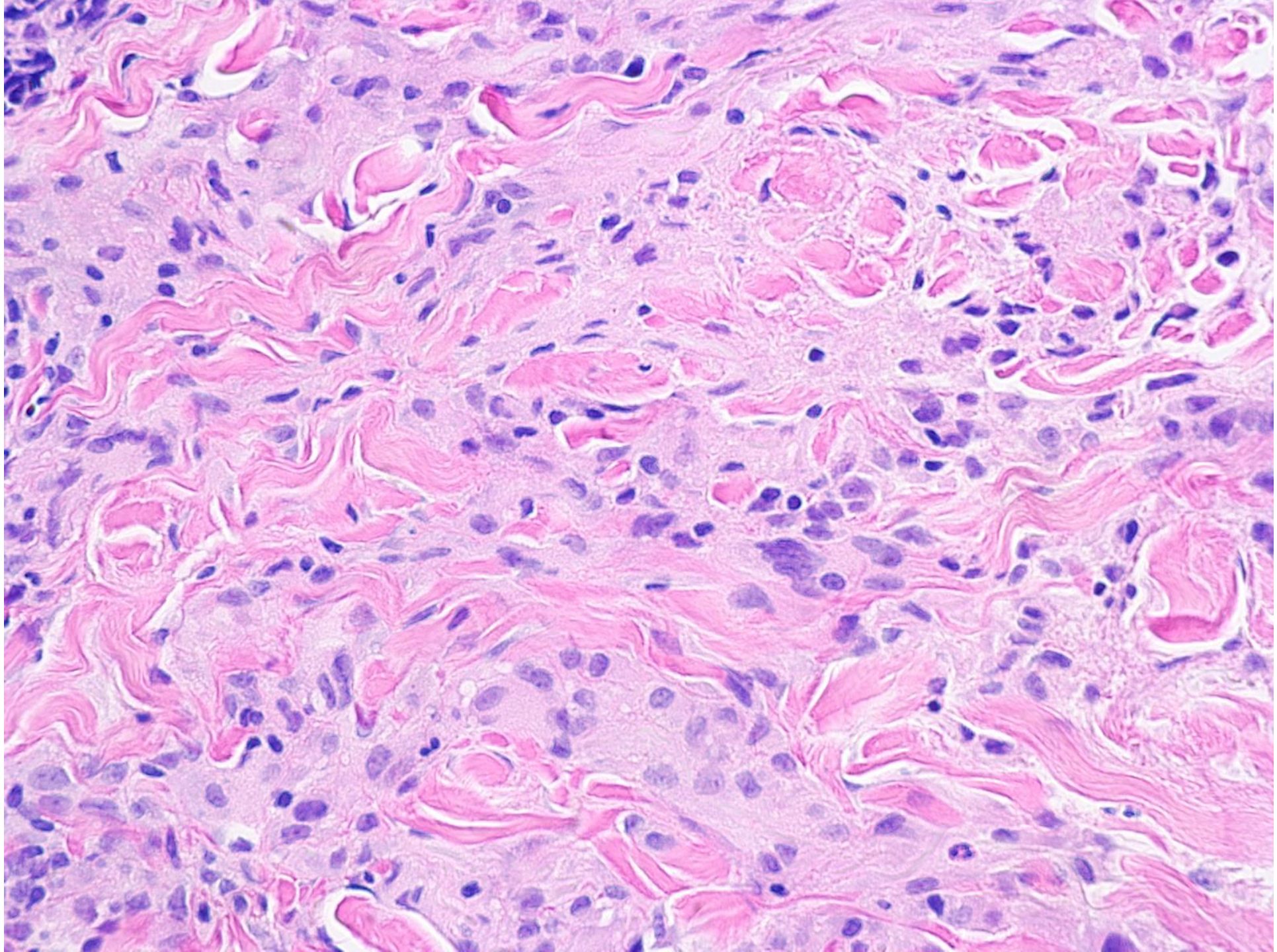
D. Granuloma annulare

E. Tuberculosis


Fite special stain







Q3. 71F, left thigh, annular papules and nodules on lower extremities; interface dermatitis vs. vasculitis

A. Sarcoidosis

B. Foreign body granuloma and reaction

C. Lepromatous leprosy

D. Granuloma annulare

E. Tuberculosis