

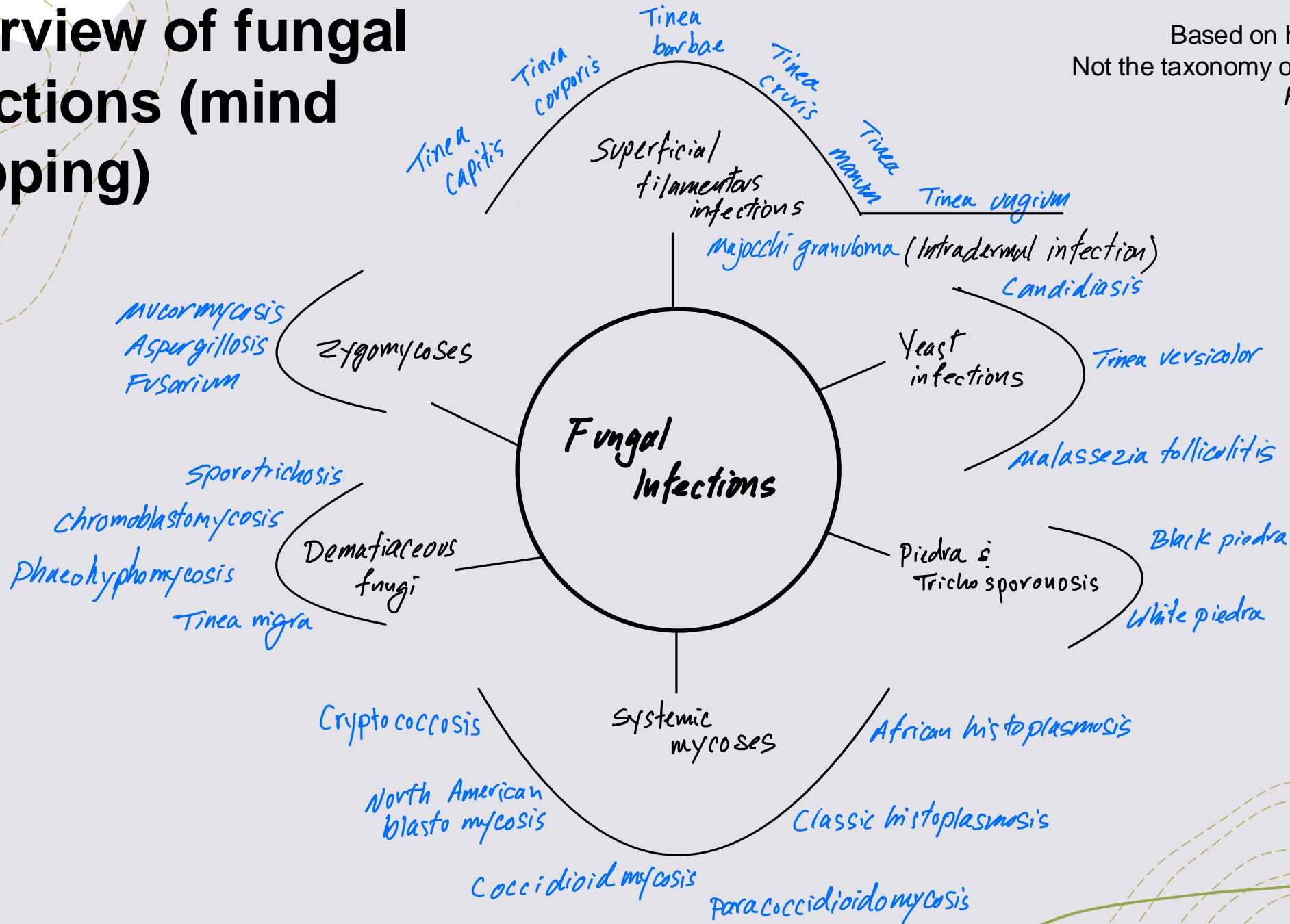


Fungal Infections

Soheil S. Dadras MD-PhD

Overview of fungal infections (mind mapping)

Based on human disease
Not the taxonomy or phylogeny of kingdom
Fungi



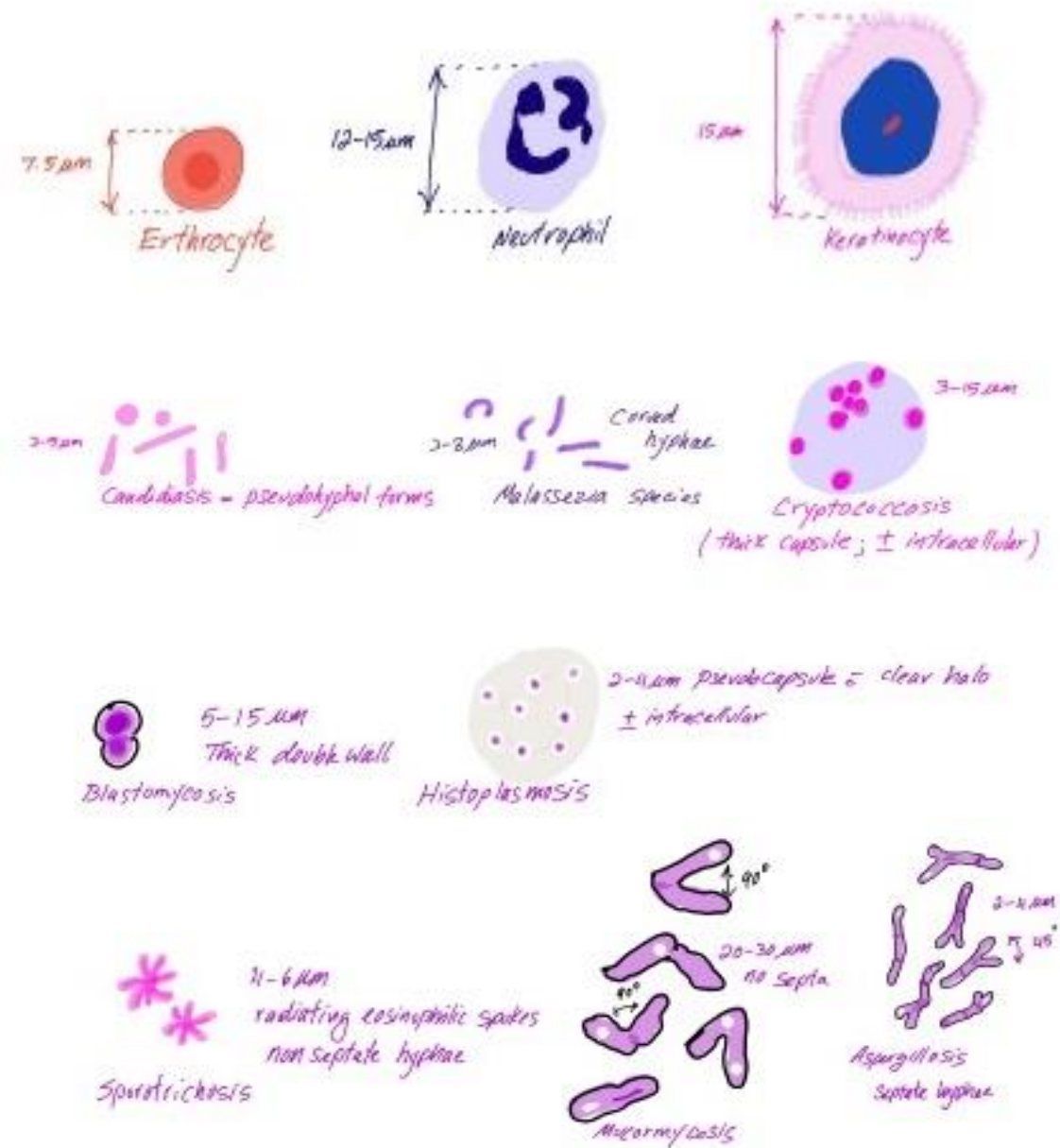
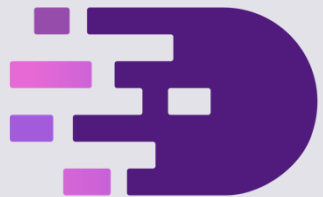
Histologic reaction to fungal infections:

Range of patterns

- + Psoriasiform spongiosis
- + Subcorneal neutrophilic pustulosis
- + Neutrophilic abscess
- + Folliculitis
- + Near – normal skin findings
- + Granulomatous reaction with mixed inflammation
- + Suppurative granuloma
- + Giant cells with microorganisms
- + Pseudoepitheliomatous hyperplasia
- + Intraepidermal and dermal neutrophilic microabscess
- + Necrosis, vascular, thrombosis, and infarction

Histologic size comparison

Morphologic guide to study fungal infections



Fungal identification

- Bed side: 10% potassium hydroxide (KOH)
- Wood lamp, e.g., *Microsporum* and *Trichophyton schoenleinii*
- Cultures rely on colonies and conidia—takes several weeks
- Histologic examination
- Special stains
 - Periodic acid-Schiff (PAS) stain with diastase
 - Gomori silver methenamine (GMS) or with Grocott's modification
- Mucicarmine or Alcian blue-PAS: *Cryptococcus neoformans*
- Fluorescence microscope: auto fluorescent species (*Blastomyces*, *Histoplasma*)
- Polymerase chain reaction (PCR)
 - Nested PCR
 - Real-time PCR
 - Limited 18S rRNA sequencing

Yeast vs. Hyphae

Open Access Review

From Jekyll to Hyde: The Yeast–Hyphal Transition of *Candida albicans*

by  Eve Wai Ling Chow¹ ,  Li Mei Pang²  and  Yue Wang^{1,3,*} 

¹ Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), 61 Biopolis Drive, Proteos, Singapore 138673, Singapore

² National Dental Centre Singapore, National Dental Research Institute Singapore (NDRIS), 5 Second Hospital Ave, Singapore 168938, Singapore

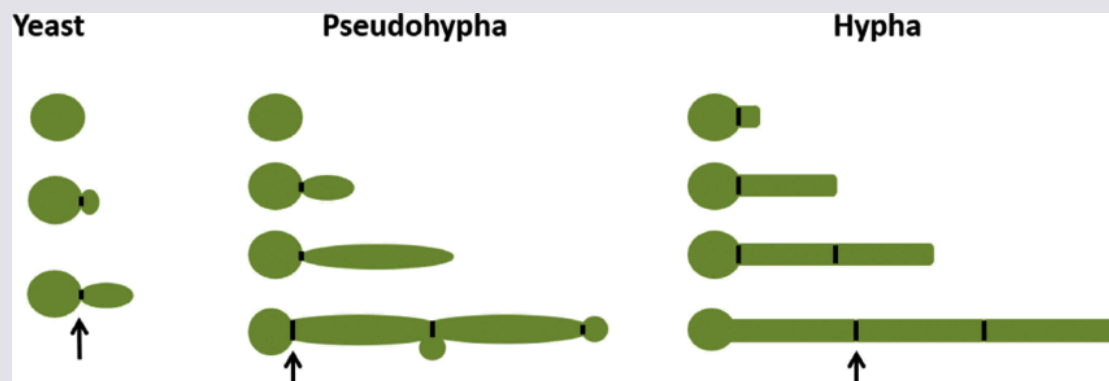
³ Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Drive, Singapore 117597, Singapore

* Author to whom correspondence should be addressed.

Pathogens **2021**, *10*(7), 859; <https://doi.org/10.3390/pathogens10070859>

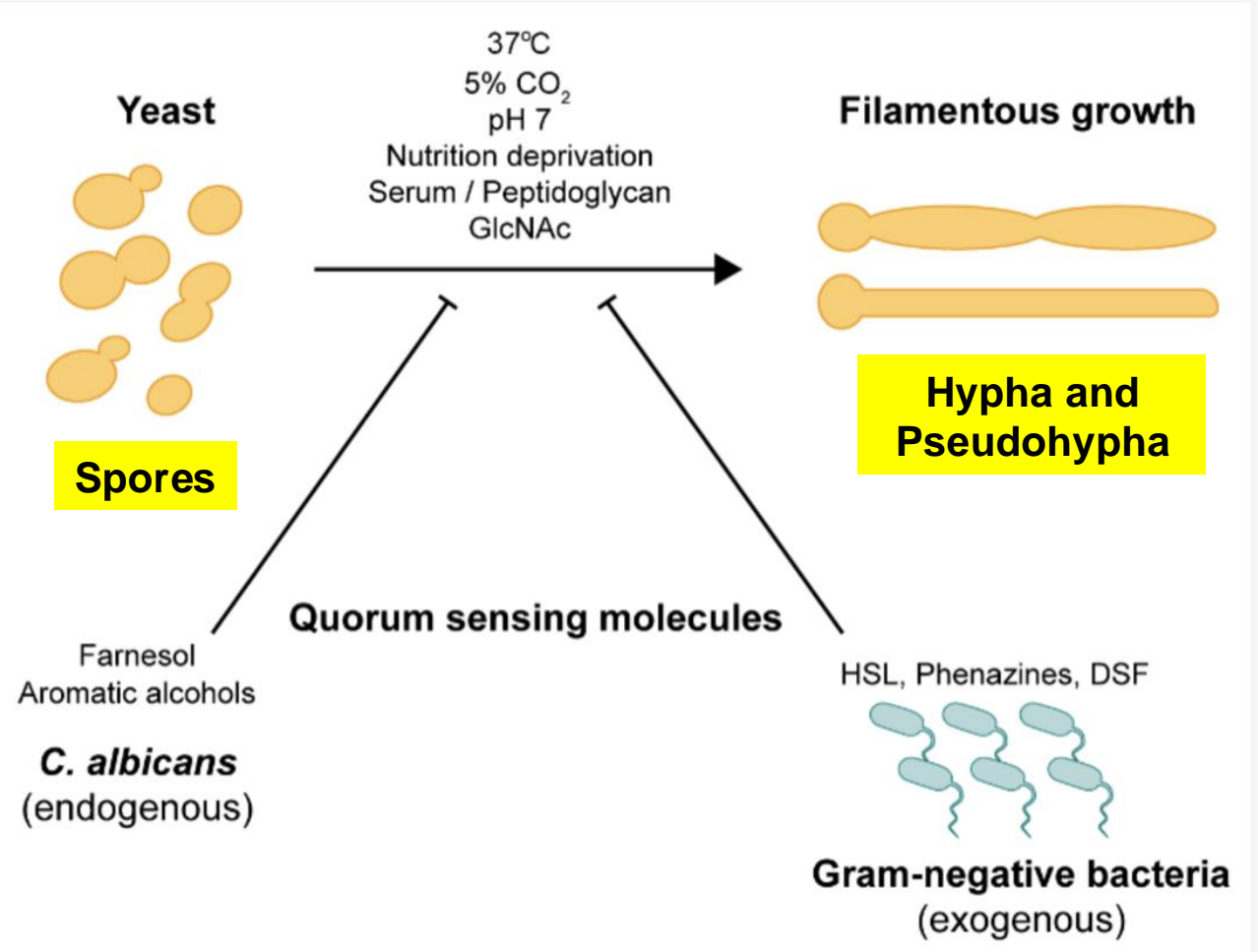
Submission received: 14 June 2021 / Revised: 30 June 2021 / Accepted: 5 July 2021 / Published: 7 July 2021

(This article belongs to the Special Issue *Candida albicans: A Major Fungal Pathogen of Humans*)



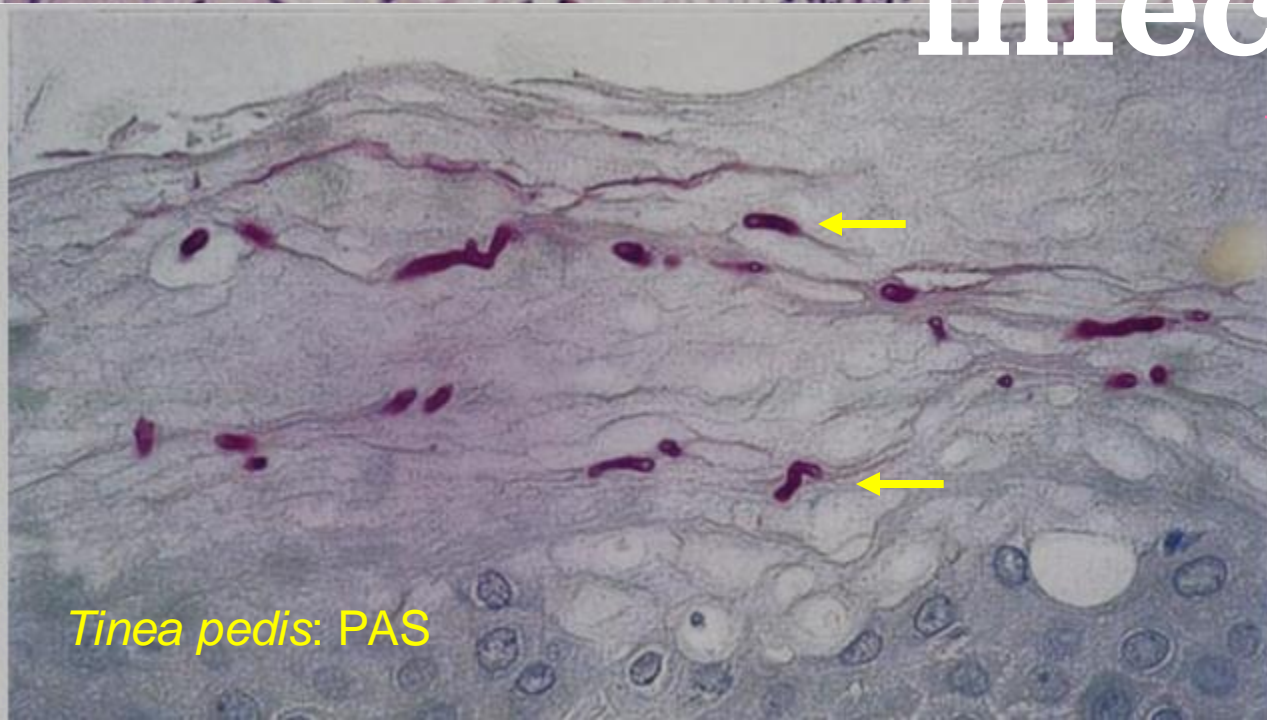
Black arrow indicate septin ring
The width of pseudohyphae cells are larger than hyphal cells

Figure 1. External hyphal-inducing signals. The yeast-to-hyphae transition in *C. albicans* can be triggered by various environmental cues such as high temperature (37 °C), high CO₂ concentration (~5%), pH 7, nutrition deprivation, serum, peptidoglycan, *N*-acetylglucosamine, and inhibited by quorum-sensing molecules from endogenous and exogenous sources.



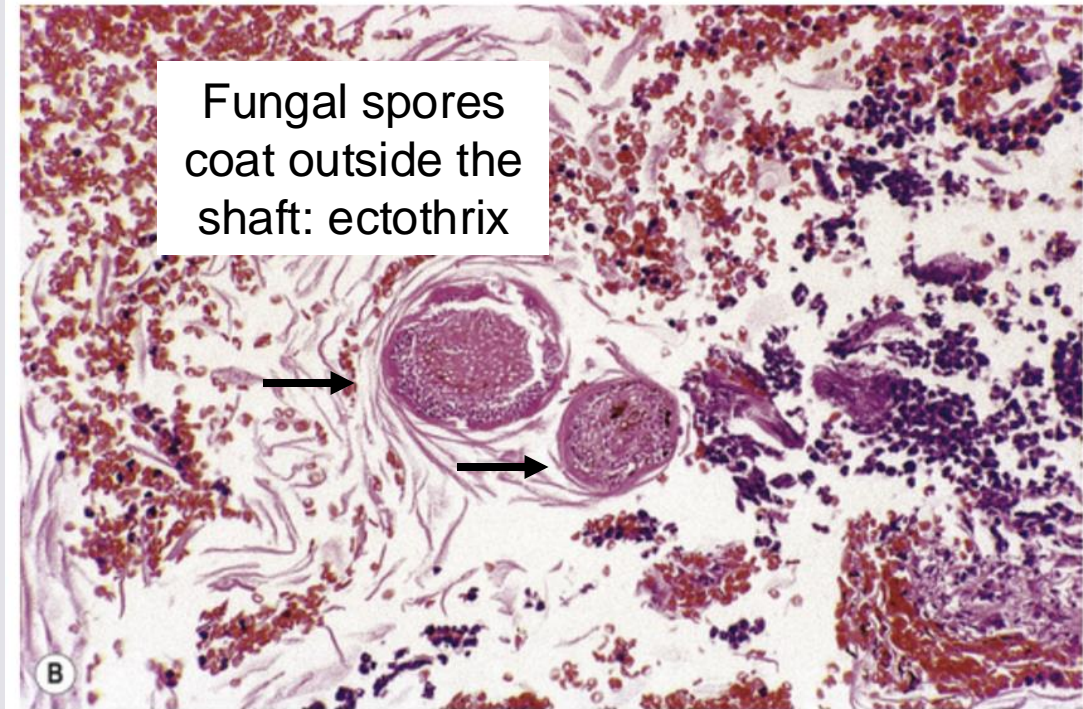
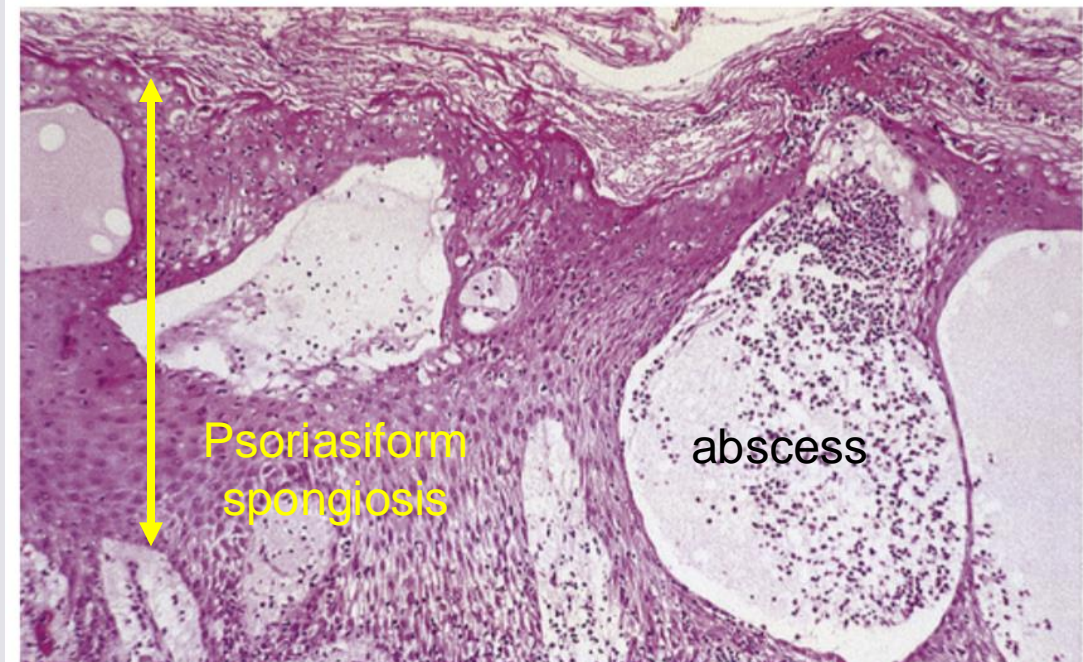


Superficial filamentous infections



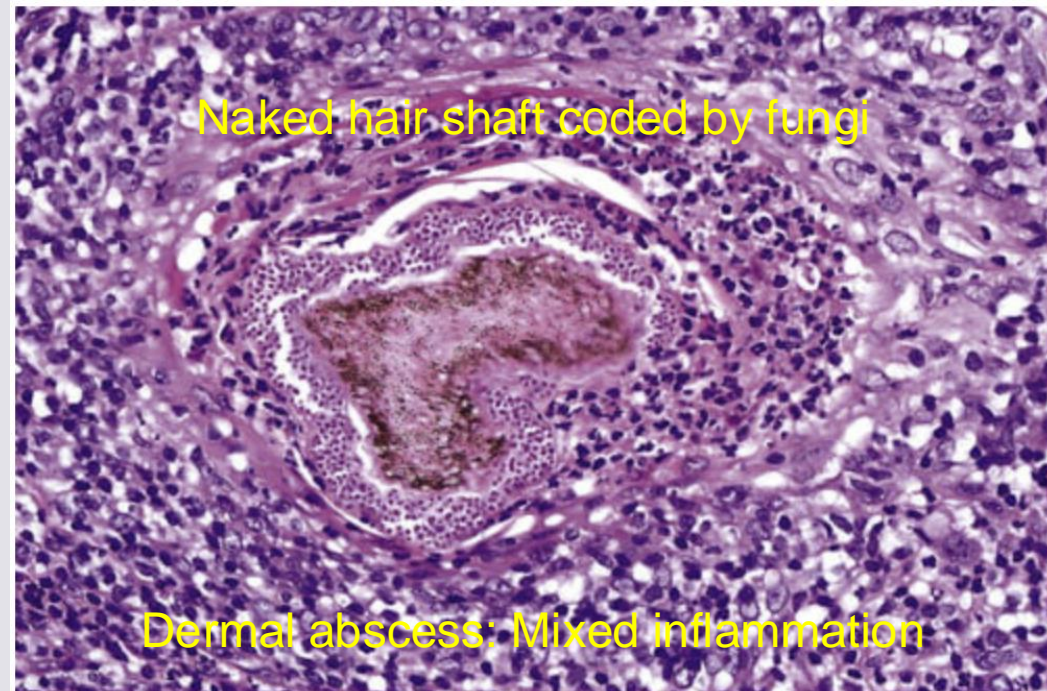
Tinea capitis

- *Trichophyton, Microsporum*
- Infections:
 - Ectothrix: small or large spore
 - Endothrix: large spore
 - Begins with hyphal invasion of hair follicles
 - May lead to kerion (boggy, pus-filled lesions)
- Matted hairs, crusting, alopecia



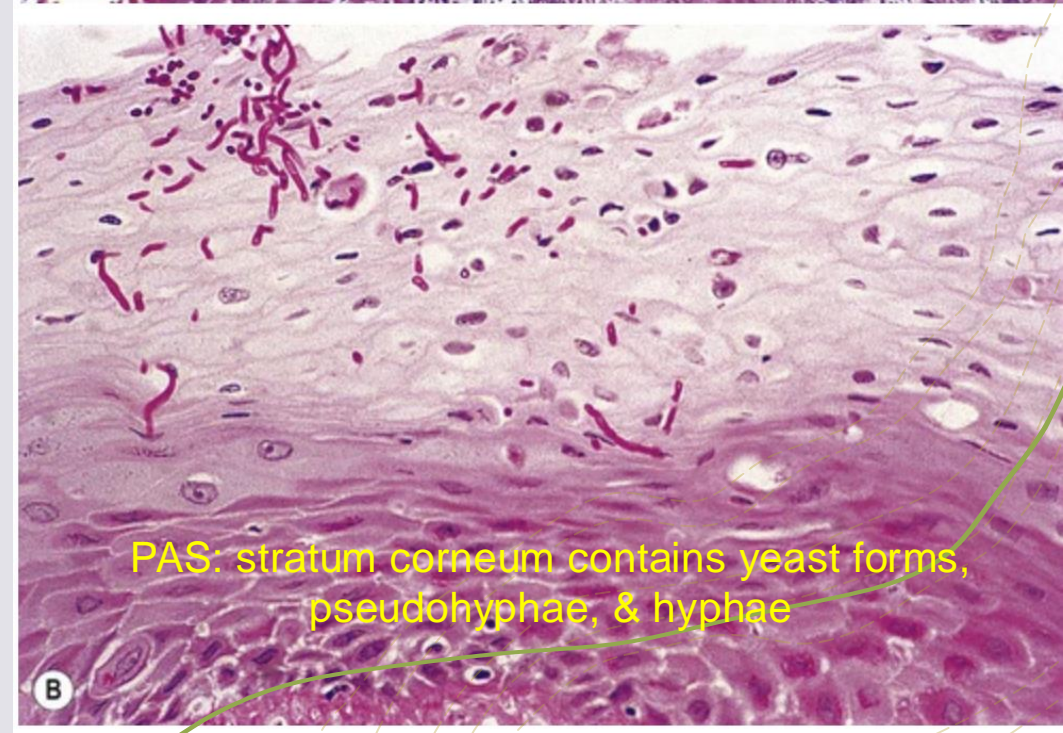
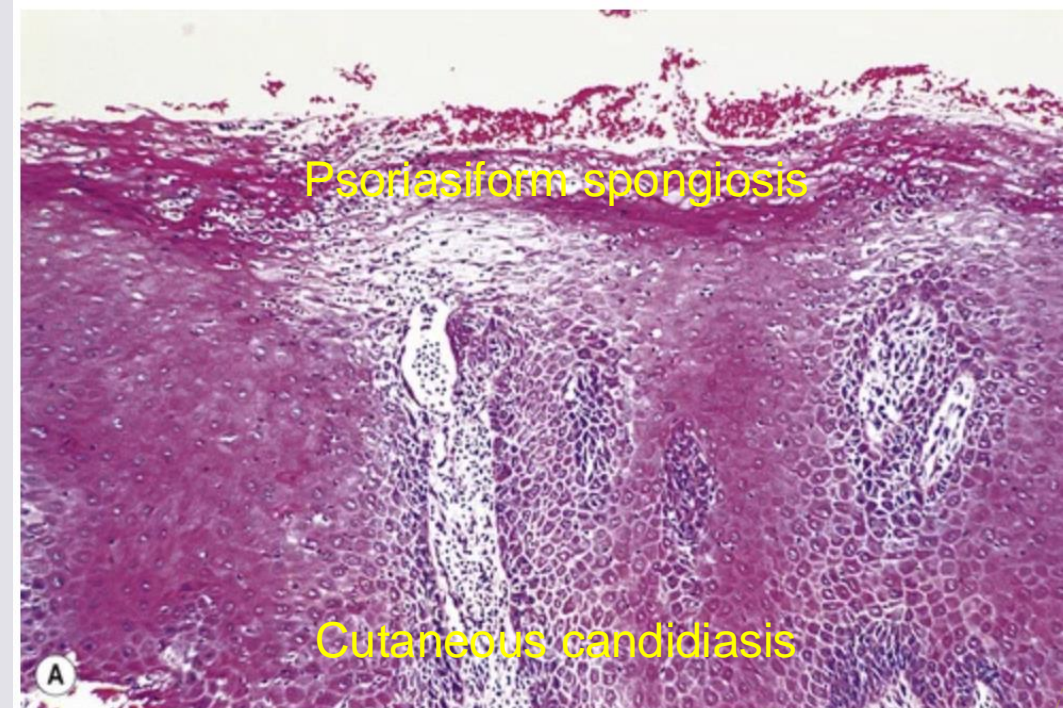
Nodular granulomatous dermatitis (Majocchi granuloma)

- Uncommon intradermal infection by dermatophytosis
- Presents clinically as granulomata, cellulitis, or plaques
- Anterior aspect of the legs
- Hyphae or spores
- Dermal neutrophilic abscess
- Organisms may be scanty or multiple
- Multiple step – leveled sections are important
- Positive: PAS, GMS



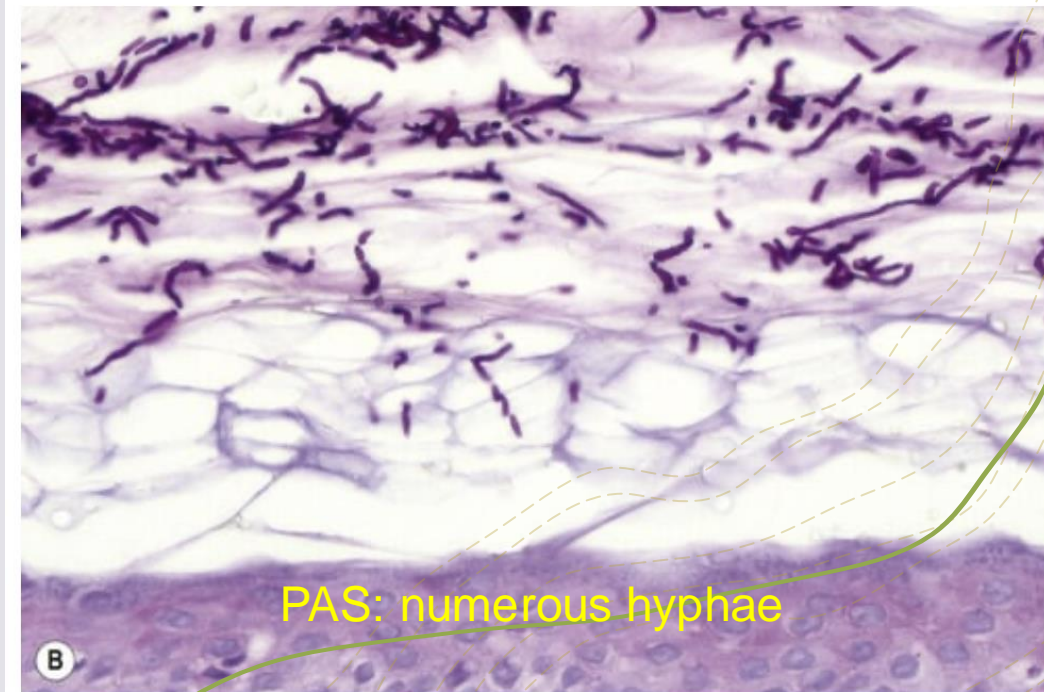
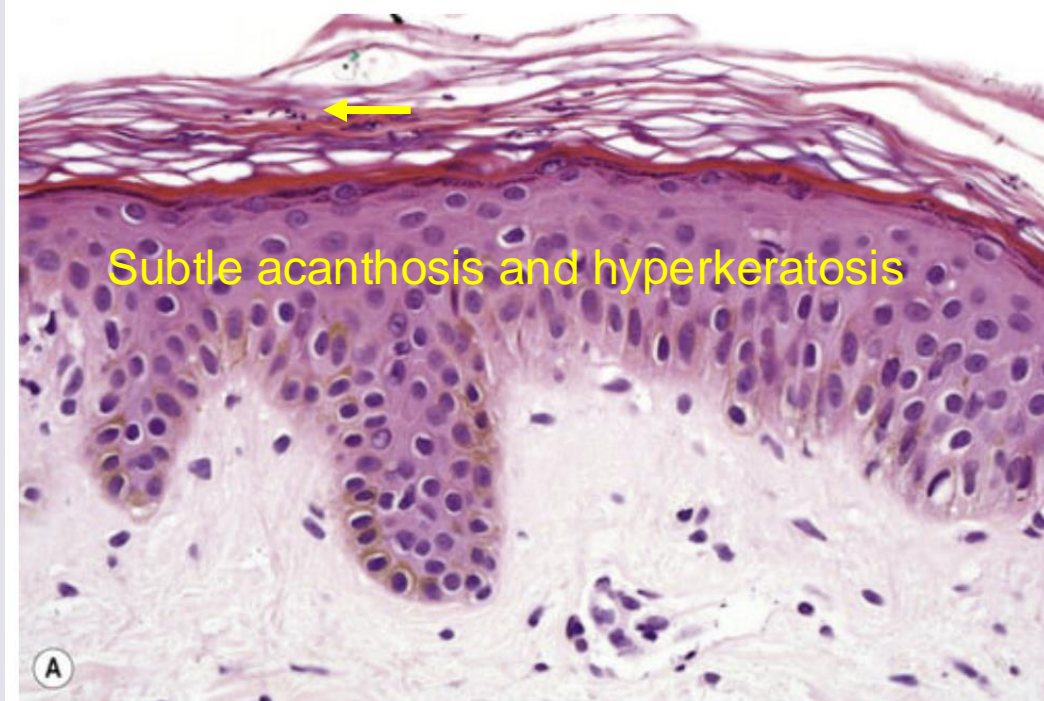
Mucocutaneous candidiasis

- Acute forms: more common in infants, elderly, pregnant, and diabetic patients
- Chronic forms: often associated with cell mediated immune deficiency
- Chronic atrophic candidiasis in denture wearers
- Disseminated: triad of fever, papular erythematous rash and myalgias in neutropenic patients (same histopathology)
- Erythema with irregular margins, moist exudates, and satellite papules
- Oral friable white plaques, easily scraped off
- Differential diagnosis: dermatophyte infection, impetigo, pustular psoriasis, and subcorneal pustular dermatitis



Tinea versicolor

- Caused by *Malassezia*
- Warm months and tropics
- Early 20s in temperate zones
- Pale to brown, scaling macules over the upper trunk
- Differential diagnosis: *tinea corporis*, candidiasis, and spongiotic dermatitis

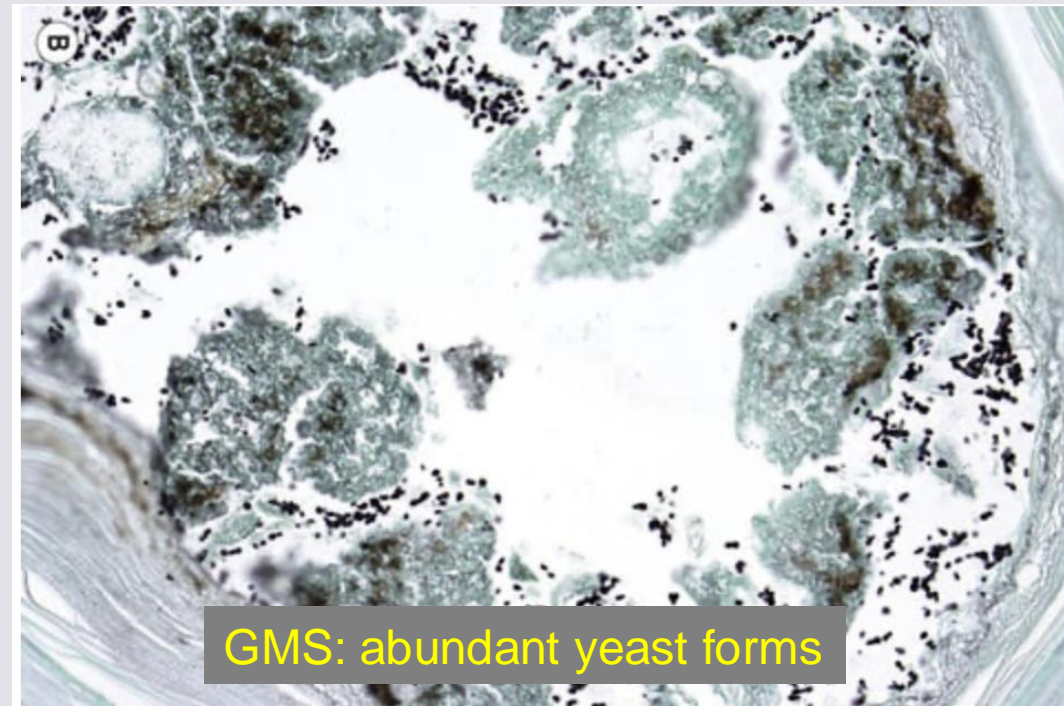


Malassezia (pityrosporum) folliculitis

- Caused by *Malassezia*
- Young to middle-aged adults
- Pruritic papules: trunk, shoulders and face
- Occlusion and greasy skin predispose to infection
- Differential diagnosis: acneiform drug eruption, dermatophytic or bacterial folliculitis, follicular mucinosis and acne



- Dilated follicle/
- Folliculitis
- Follicular plug
- Neutrophils, lymphocytes, histiocytes in and around follicles
- Foreign body reaction
- Pools of mucin



GMS: abundant yeast forms

Piedra (stone) and Trichosporonosis

	Black Piedra	White Piedra
Causing species	<i>Piedra hortae</i>	<i>Trichosporon</i>
Environment	Tropics	Semitropical, temperate
Anatomic areas	Scalp	Beard, axillary, or groin hairs
Color	Hard, dark	Soft, light
Adherent nodules	Tight	Easily scraped off
Skin & hair follicles	Normal	Normal
Hair breakage	No	Yes
	Dark hyphae & spores	Blastoconida, arthroconida
DDX	Pediculosis, trichomycosis, trichorrexis, monilethrix	

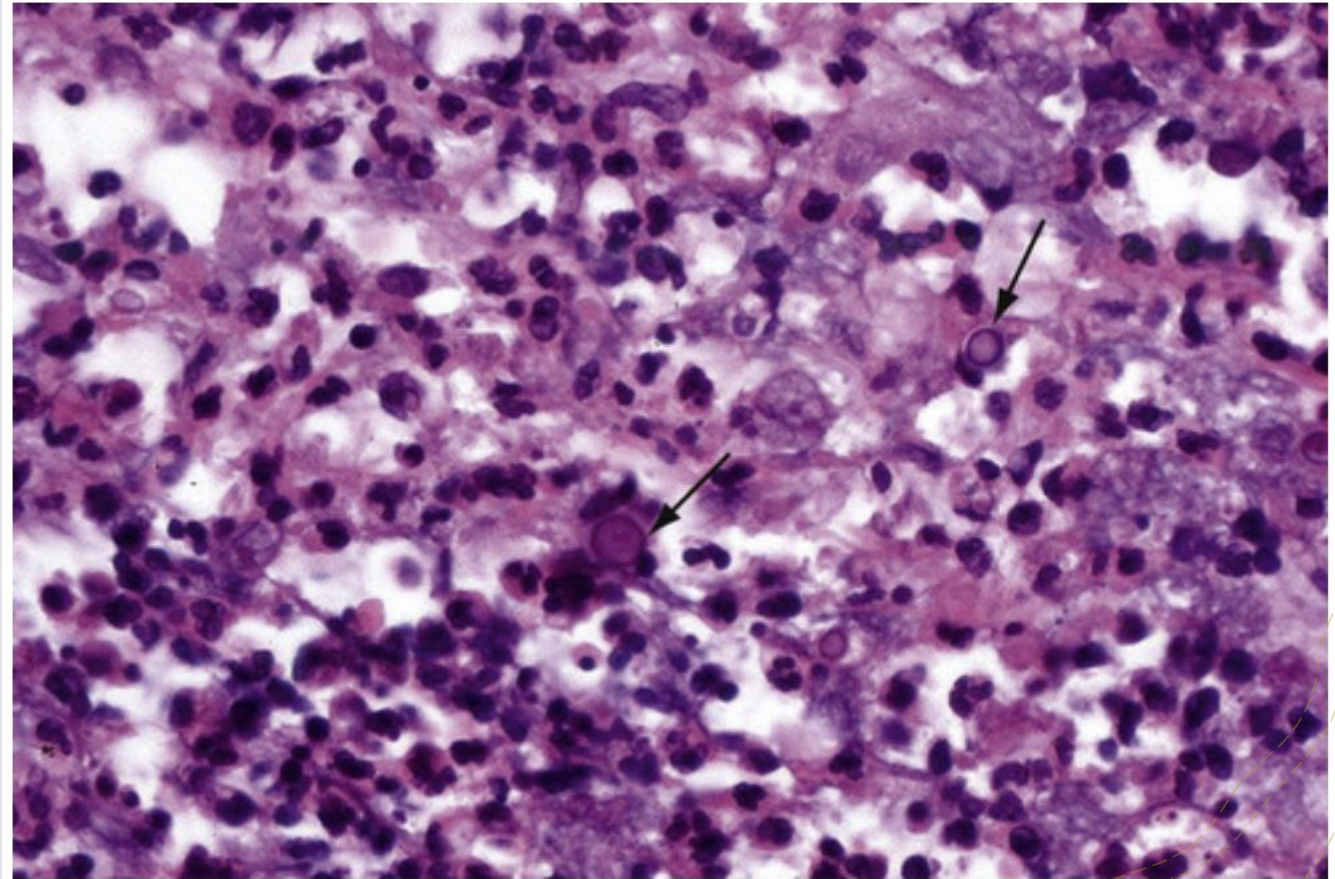


Black Piedra: brown nodule attached to hair shaft

Hair pull with KOH prep
Skin biopsy: normal

Systemic mycoses

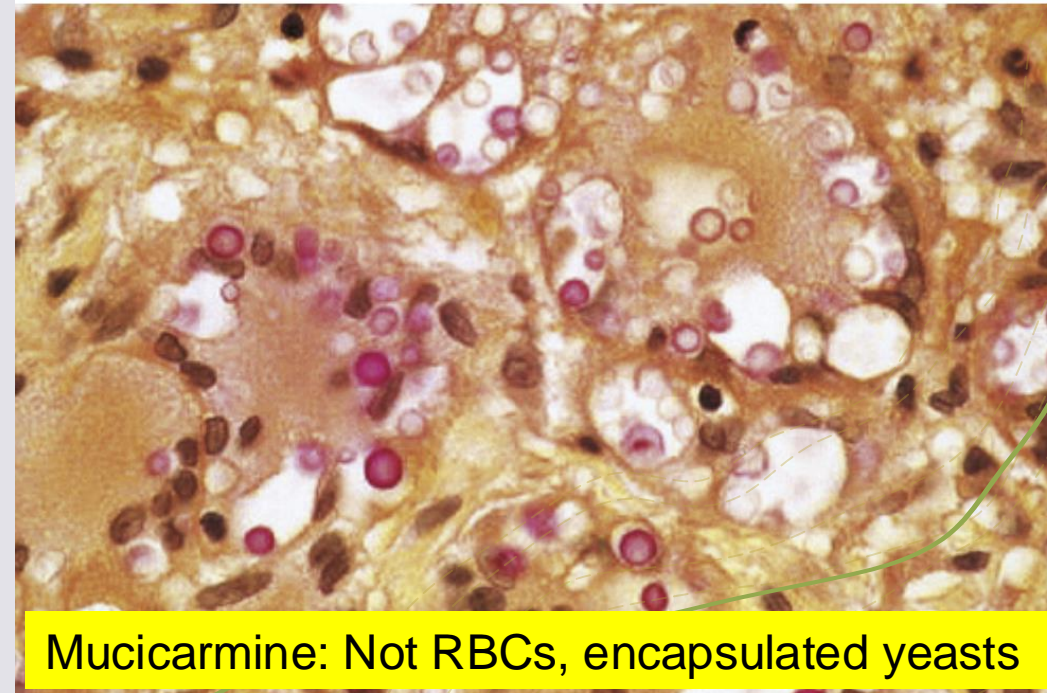
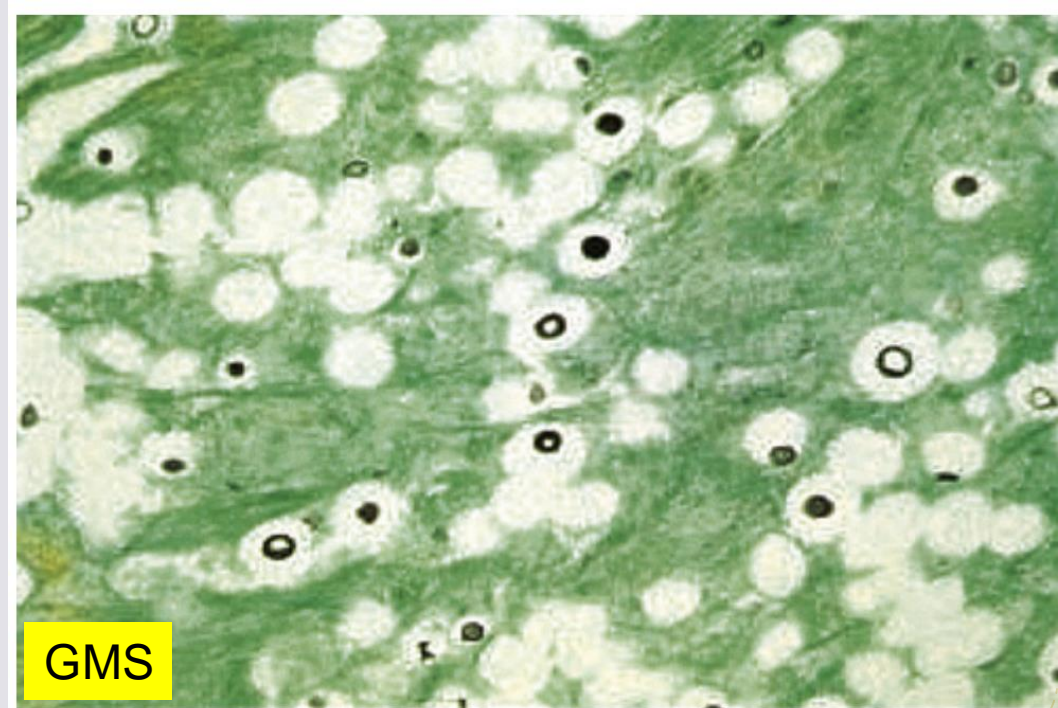
- + The infection is respiratory
- + Can spread due to failure of normal cell – mediated immune response or reactivation of dormant sites
- + Mucocutaneous lesions can occur in 10% of patients with disseminated disease
- + Skin lesions are essentially diagnostic of systemic disease because primary cutaneous infection is exceedingly rare
- + Cryptococcosis, coccidiomycosis, and histoplasmosis



Cryptococcosis: Multiple yeast forms in a patient receiving corticosteroid therapy for lupus

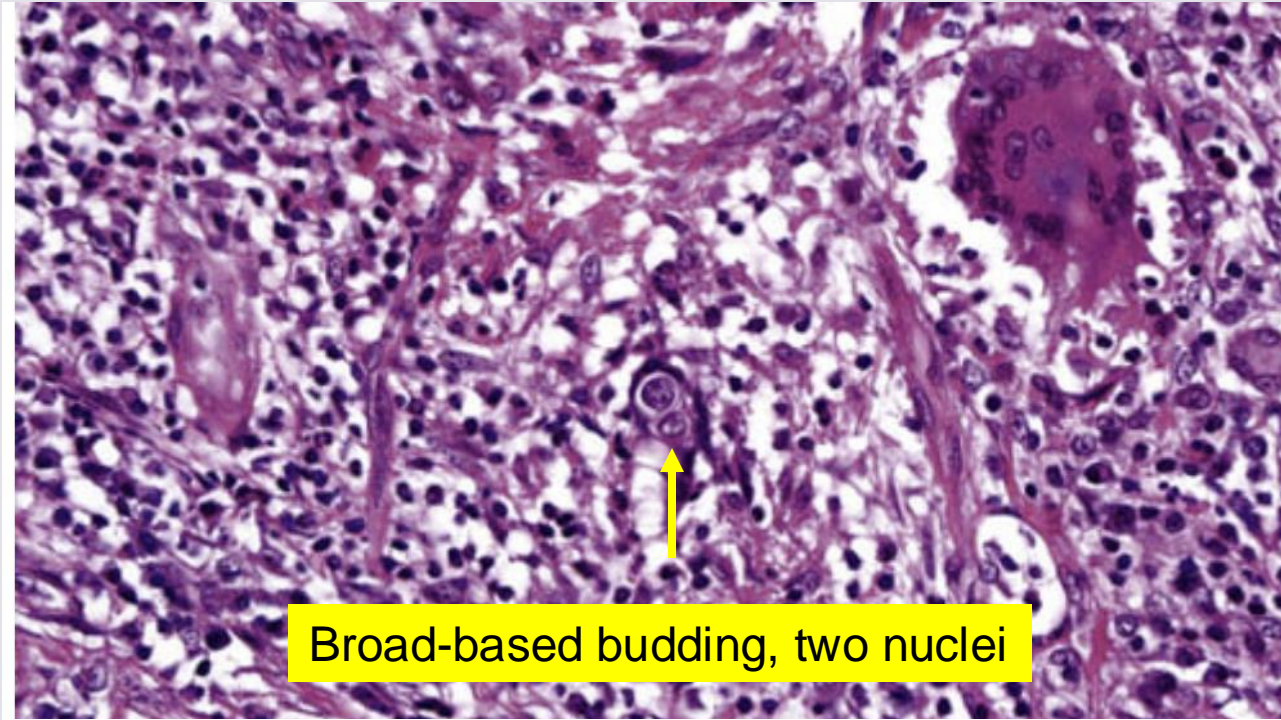
- + Caused by *Cryptococcus neoformans*
- + Found in soil contaminated with bird and bat excreta
- + Usually inhaled, can disseminate to brain, meninges, and cerebral fluid
- + Skin lesions: papules, pustules, nodules, and cellulitis.
- + Most common systemic, fungal infection in AIDS patients
- + Large aggregate of encapsulated budding refractile least 5 to 15 μm in diameter
- + Granulomatous inflammation of lymphocytes, neutrophils, histiocytes, and multinucleated giant cells
- + Intracellular (within macrophages)
- + Positive for PAS, GMS, and Fontana-Masson
- + Alcian blue and mucicarmine stain capsule
- + Differential diagnosis: blastomycosis, histoplasmosis, global mycosis

Cryptococcosis

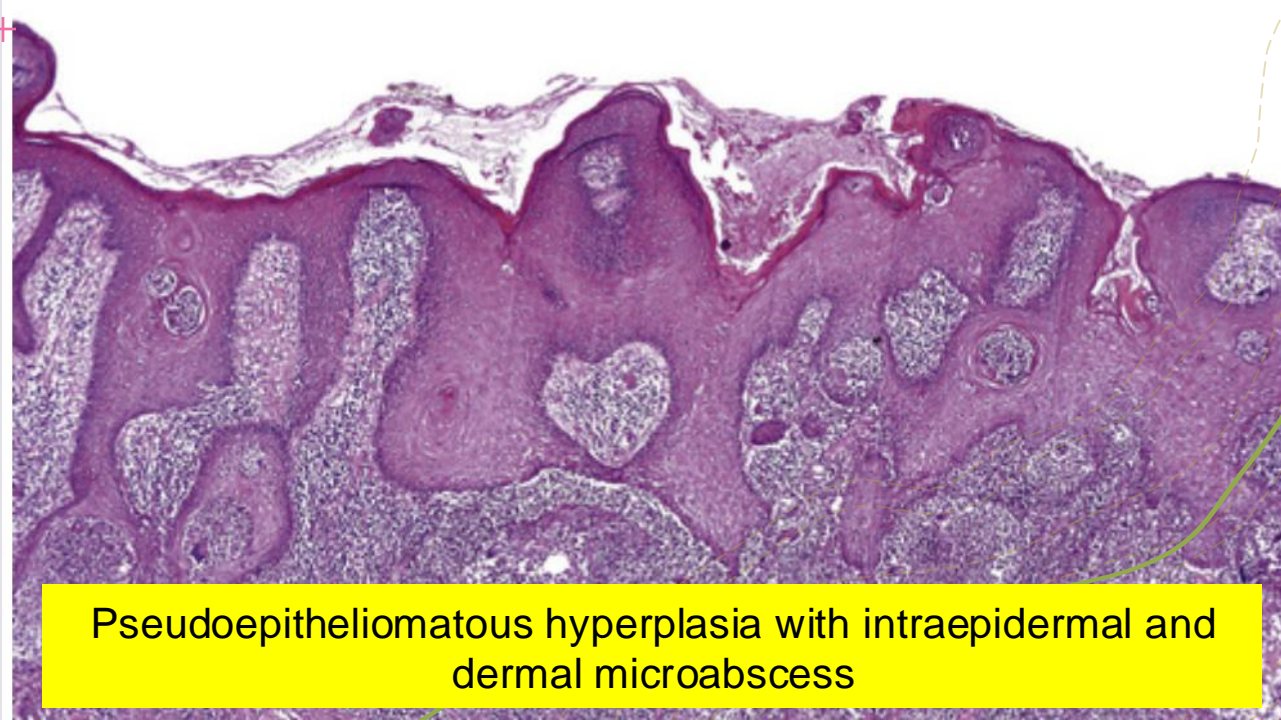


- + *Blastomyces dermatitidis*
- + Dimorphic fungus, acid soil in wooded areas
- + Endemic in South Central and Southeastern US
- + Outdoor exposure, men 20-50 to years of age
- + Cutaneous involvement in 70% of patients with disseminated disease
- + Verrucous plaques with peripheral pustules: face and mucosa
- + Suppurative granulomatous infiltrate with giant cells
- + Pseudoepitheliomatous hyperplasia with intraepidermal and dermal microabscess
- + Spores: thick-walled and 5–15 μm in diameter
- + Can be with giant cells and abscess.
- + Differential diagnosis: coccidiomycosis, tuberculosis, paracoccidiomycosis, chromoblastomycosis, blastomycosis – like pyoderma, pyoderma gangrenosum, and halogenoderma

North American blastomycosis



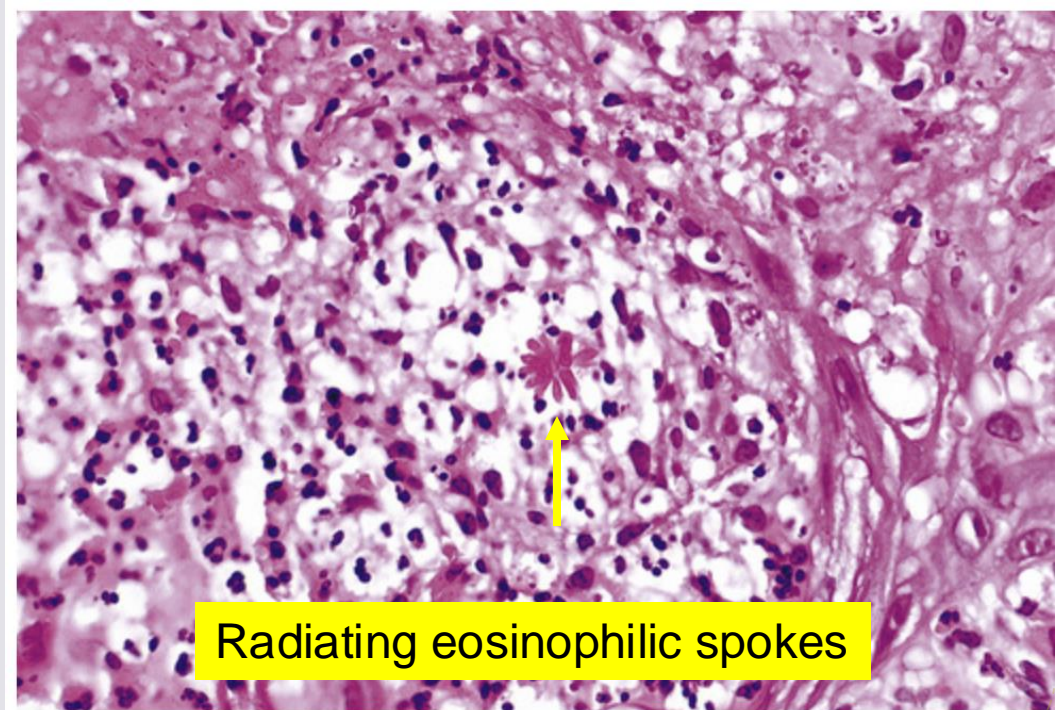
Broad-based budding, two nuclei



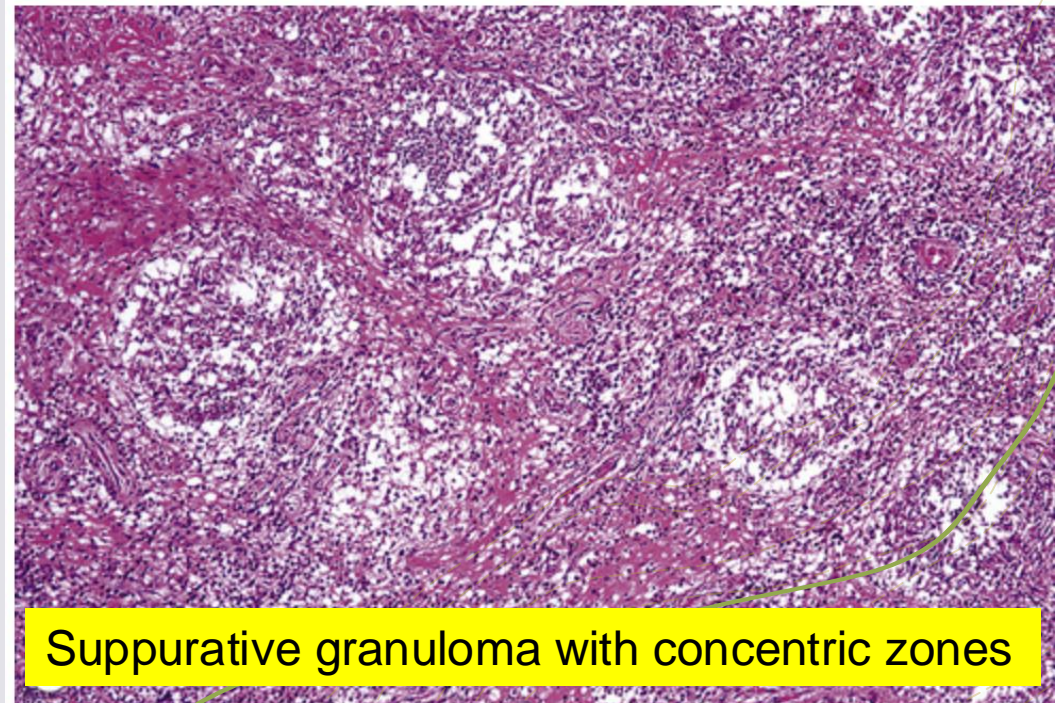
Pseudoepitheliomatous hyperplasia with intraepidermal and dermal microabscess

- + *Sporothrix Schenckii*
- + Trauma inoculates into skin --> cutaneous/subcutaneous nodules, involvement of lymphatics
- + Three forms: lymphocutaneous, fixed cutaneous, and disseminated
- + Early: non-specific infiltrate of lymphocytes, neutrophils, and plasma cells
- + Established:
 - + Pseudoepitheliomatous hyperplasia
 - + Suppurative granuloma with concentric zones
 - + Neutrophilic microabscess centrally
- + Organisms difficult to find in tissue:
 - + 4–6 μm around/oval or 8 μm , cigar – shaped forms
 - + Multiple buds, asteroid bodies
 - + Rare, branching, non-septate hyphae
- + Differential diagnosis: other infections (deep fungi, atypical mycobacteria, blastomycosis, – like pyoderma), halogenoderma, pyoderma gangrenosum, and systemic vasculitis (Wagener granulomatosis)

Dematiaceous fungi: Sporotrichosis



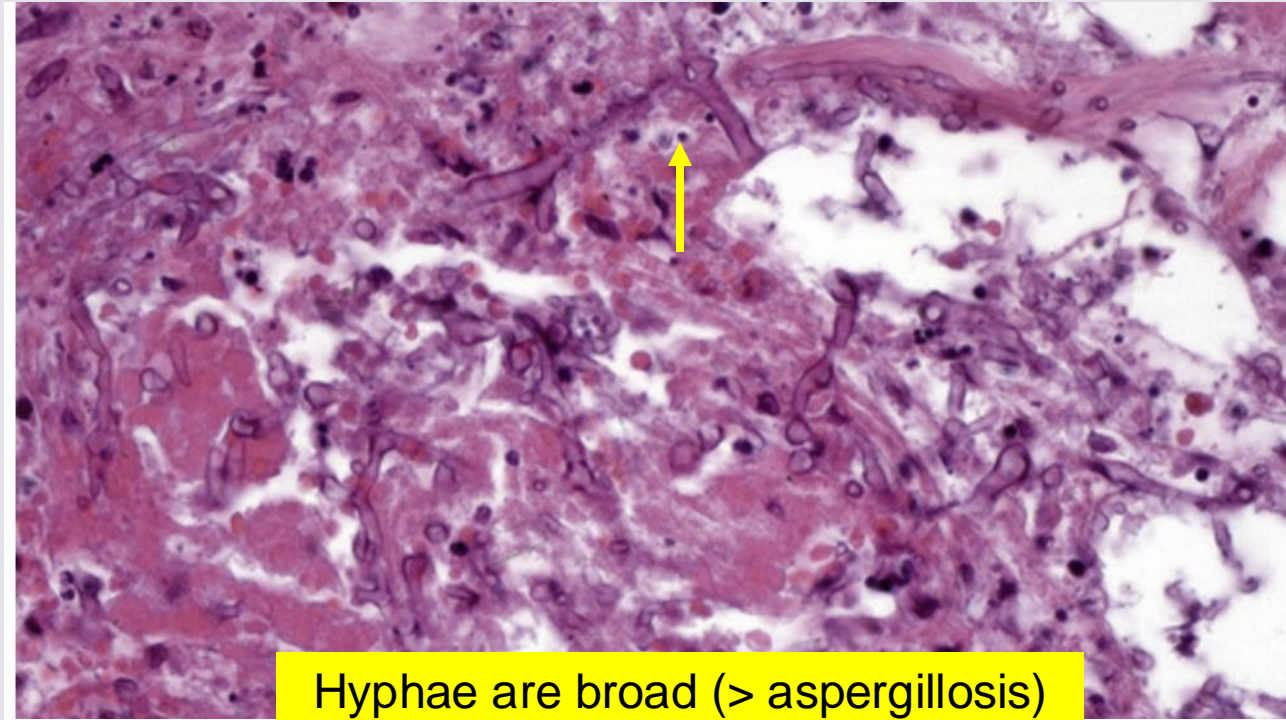
Radiating eosinophilic spokes



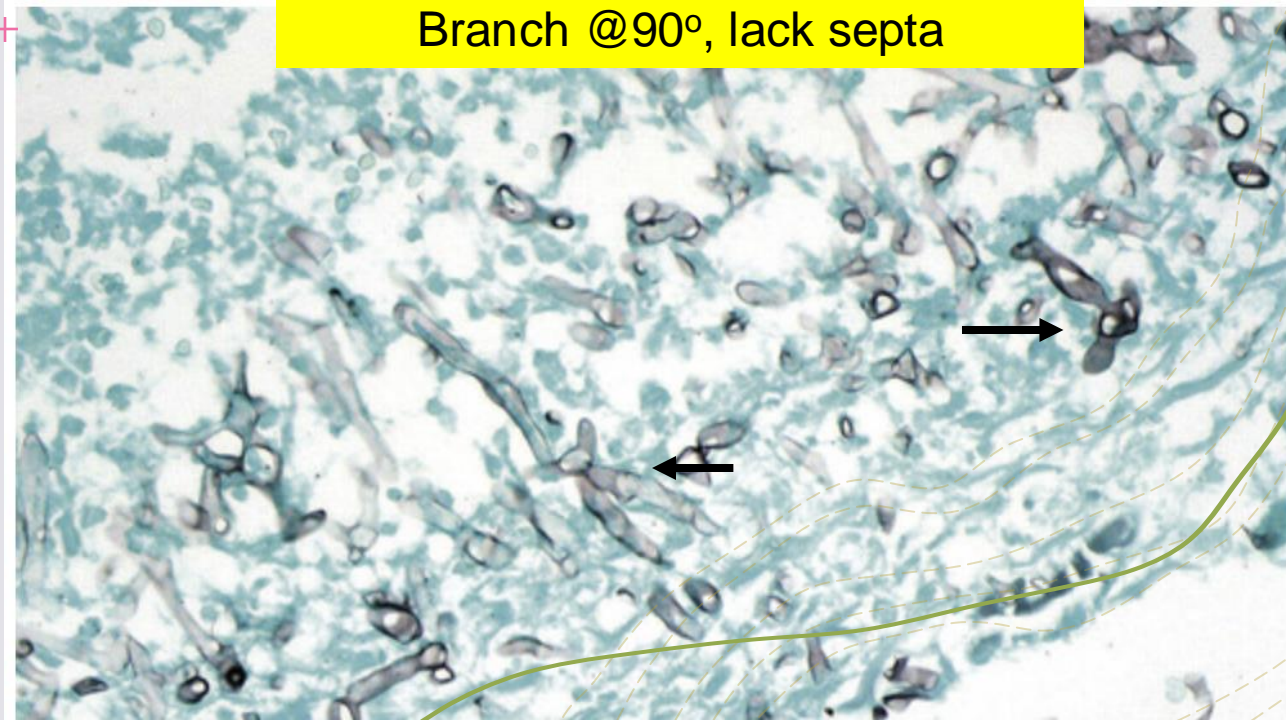
Suppurative granuloma with concentric zones

Mucormycosis

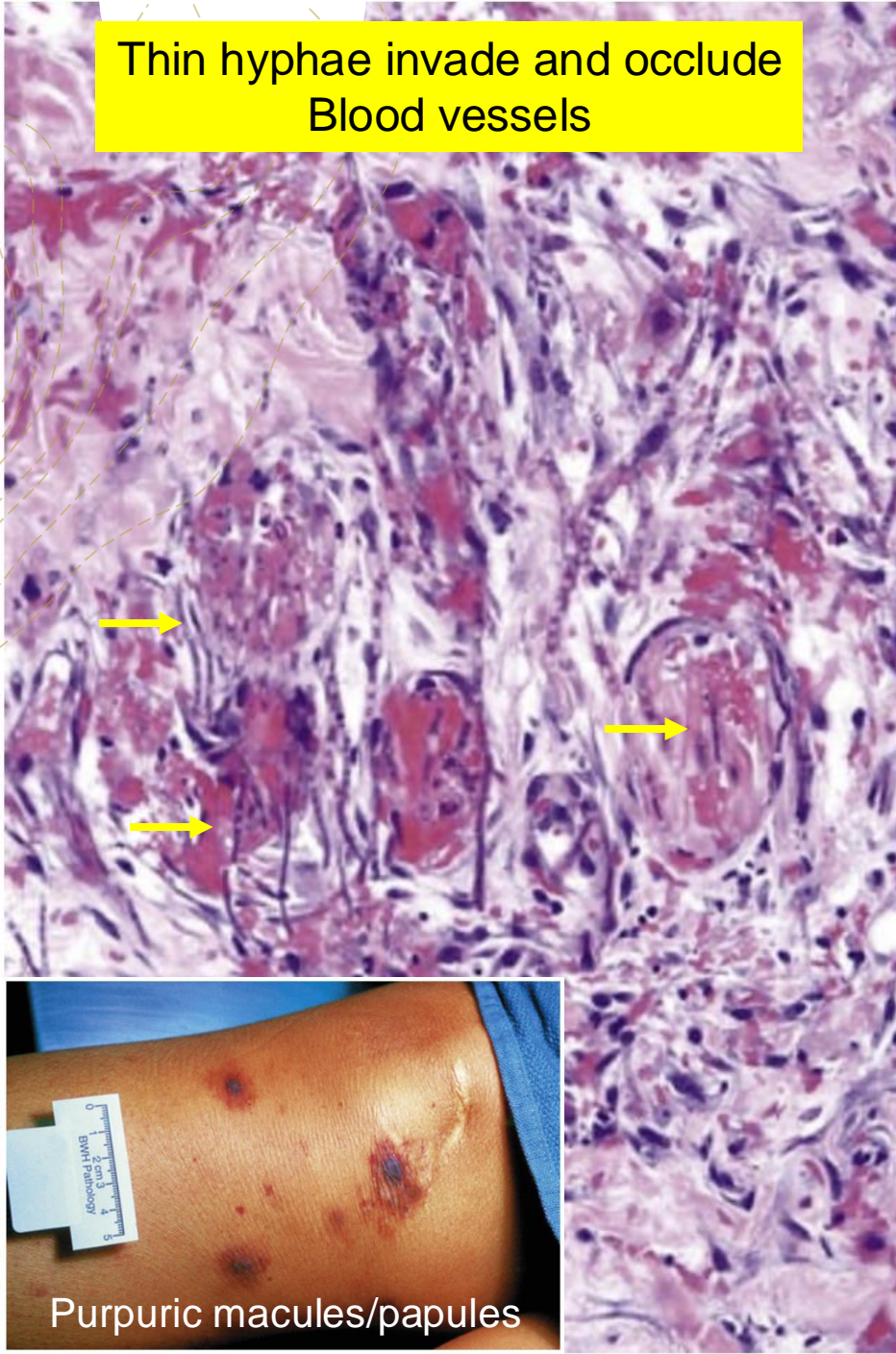
- + *Rhizopus*, *Absidia*, and *Mucor*
- + Risk factors: diabetes, leukemia, neutropenia, skin, ulceration, burns, and use of adhesive tape
- + Ecthyma-like necrotic crust surrounded by cellulitis
- + Necrosis, thrombosis, infarction
- + Large, broad, 30 μm in diameter hyphae
- + Hyphae branch at 90°, lack septa
- + Angioinvasive, present in vessel walls
- + Differential diagnosis: aspergillosis, gouty panniculitis and pancreatic panniculitis



Hyphae are broad (> aspergillosis)
Branch @90°, lack septa



Thin hyphae invade and occlude
Blood vessels



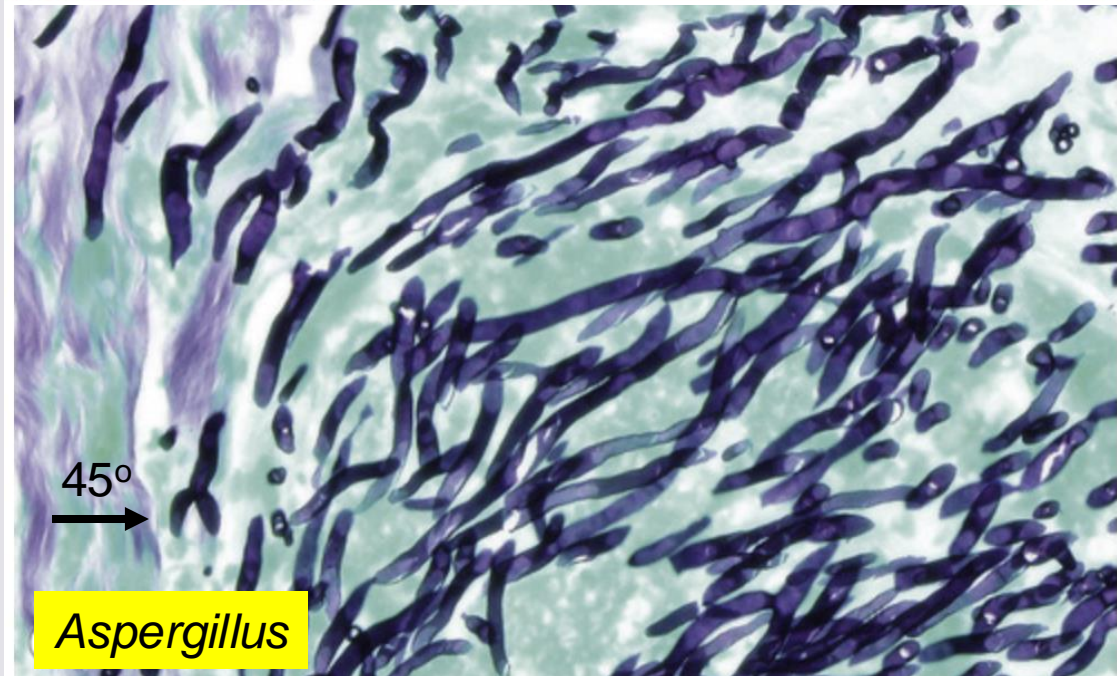
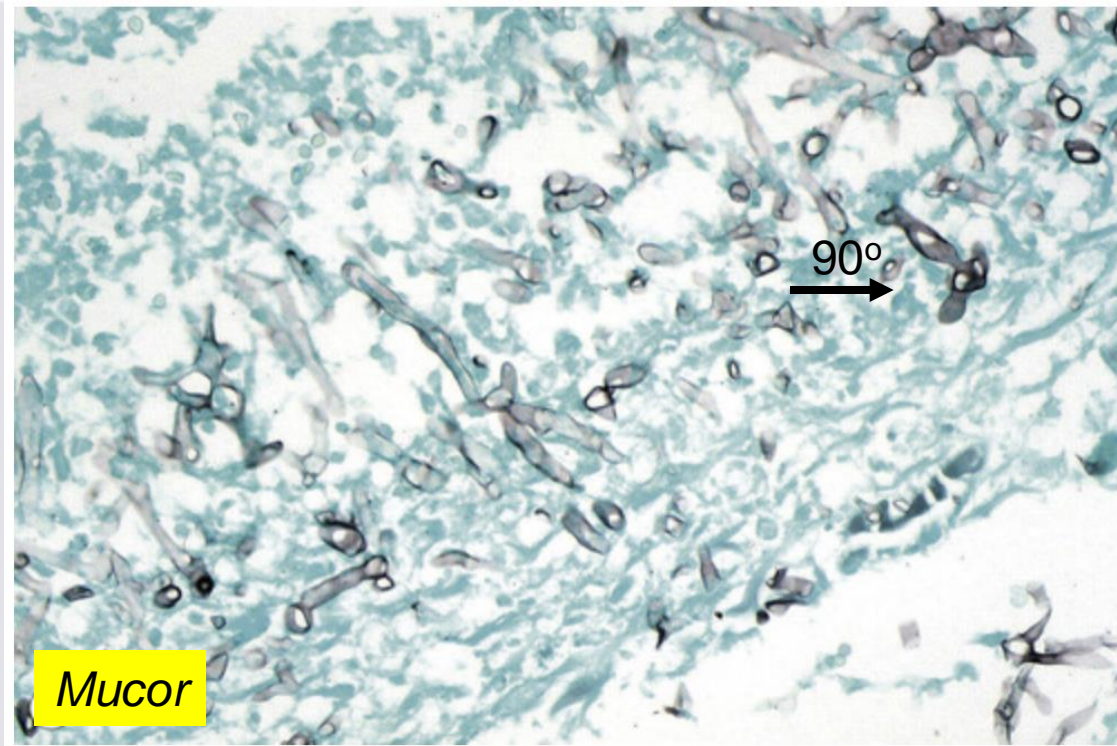
Purpuric macules/papules

Aspergillosis

- + *Aspergillus flavus*, *A. niger* and *A. fumigatus*
- + Risk factors: neutropenia, hematologic, malignancy, organ transplantation (immunosuppression), chronic granulomatous disease
- + Primary cutaneous lesions: burn, catheter sites, hospital construction dust, and adhesive tape
- + Ecthyma-like papule with central necrosis
- + Portal of entry: Lungs -> disseminated disease (5–11%)
- + Metastases: necrotizing plaques, subcutaneous granuloma or abscesses, maculopapular eruption, ecthyma
- + Septate 2–4 μm diameter, branch at 45° angle, dichotomous
- + granulomatous infiltrate with neutrophils, lymphocytes, histiocytes, and giant cells
- + Angioinvasive, present in vessel walls
- + Differential diagnosis: *Mucor*

***Aspergillus* vs. *Mucor*:** **both angioinvasive**

	<i>Aspergillus</i>	<i>Mucor</i>
Septa	Present	Absent
Diameter	2-4 μm	< 30 μm
Hyphae branch @	45°	90°
Morphology	Dichotomous	Bulbous lateral protrusion



What is the expected histopathologic reaction pattern in Piedra infection?

- A. Neutrophilic pustules
- B. Granulomatous inflammation
- C. Normal
- D. Granulomatous inflammation with pustules
- E. Ulcer with necrosis

Piedra (stone) and Trichosporonosis

	Black Piedra	White Piedra
Causing species	<i>Piedra hortae</i>	<i>Trichosporon</i>
Environment	Tropics	Semitropical, temperate
Anatomic areas	Scalp	Beard, axillary, or groin hairs
Color	Hard, dark	Soft, light
Adherent nodules	Tight	Easily scraped off
Skin & hair follicles	Normal	Normal
Hair breakage	No	Yes
	Dark hyphae & spores	Blastoconida, arthroconida
DDX	Pediculosis, trichomycosis, trichorrexis, monilethrix	



Black Piedra: brown nodule attached to hair shaft

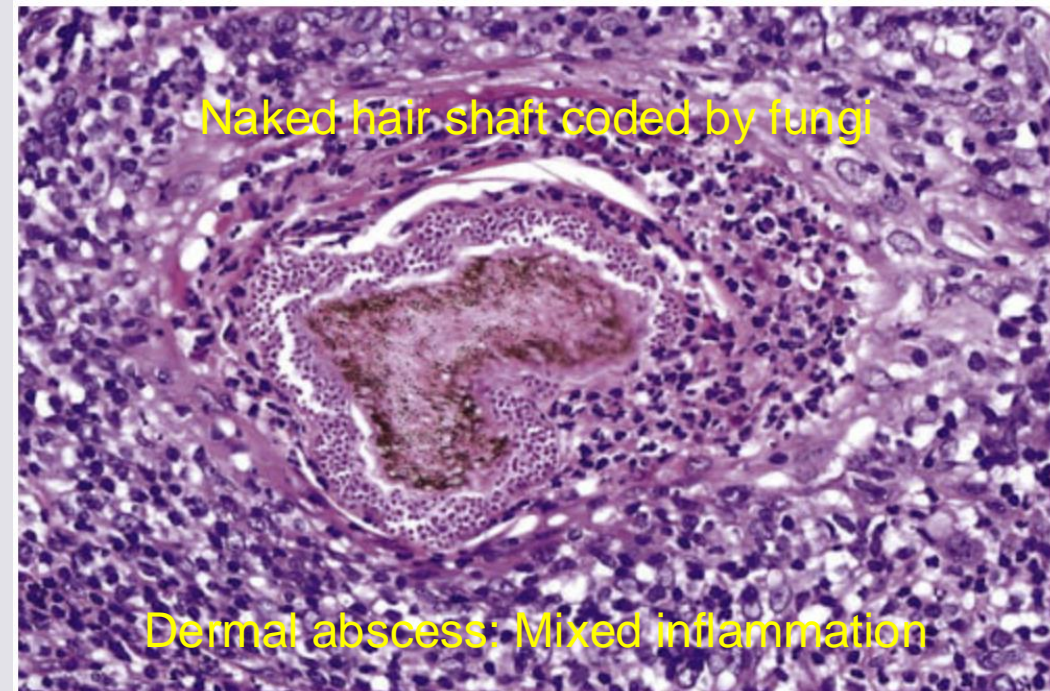
Hair pull with KOH prep
Skin biopsy: normal

What is the expected histopathologic reaction pattern in Majocchi granuloma?

- A. Dermal neutrophilic abscess
- B. Granulomatous inflammation
- C. Normal
- D. Granulomatous inflammation with pustules
- E. Ulcer with necrosis

Nodular granulomatous dermatitis (Majocchi granuloma)

- Uncommon intradermal infection by dermatophytosis
- Presents clinically as granulomata, cellulitis, or plaques
- Anterior aspect of the legs
- Hyphae or spores
- Dermal neutrophilic abscess
- Organisms may be scanty or multiple
- Multiple step – leveled sections are important
- PAS, GMS



1. Which fungal species is angioinvasive?
Aspergillus or *Mucor*?

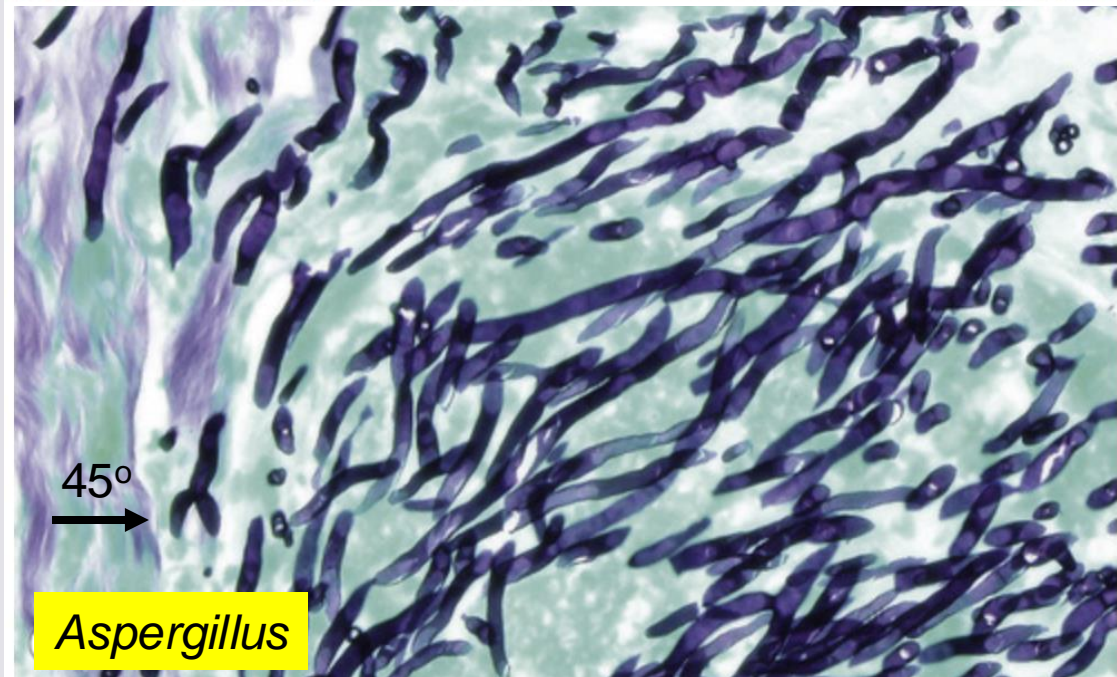
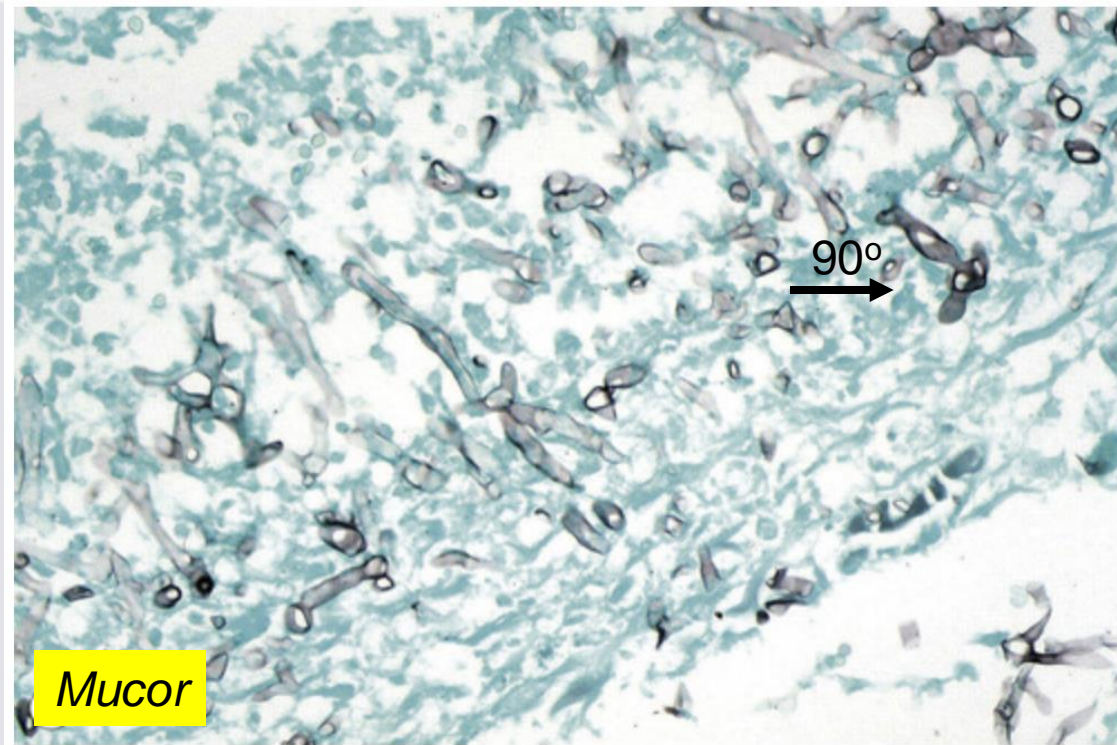
2. Which fungal species displays septa?
Aspergillus or *Mucor*?

3. Which fungal species displays 90°
hyphae branch? *Aspergillus* or *Mucor*?

4. Which fungal species displays
dichotomous morphology? *Aspergillus* or
Mucor?

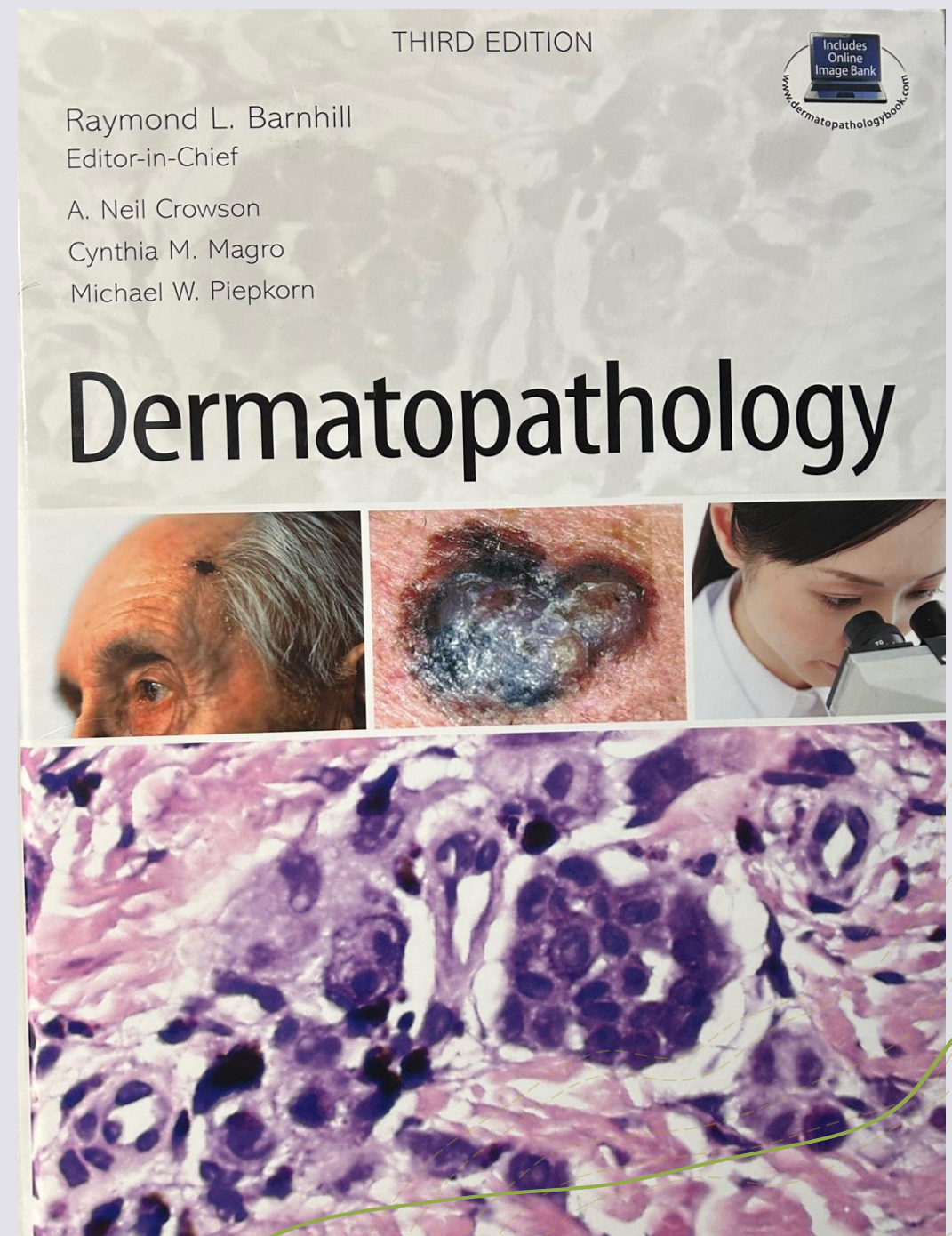
***Aspergillus* vs. *Mucor*:** **both angioinvasive**

	<i>Aspergillus</i>	<i>Mucor</i>
Septa	Present	Absent
Diameter	2-4 μm	< 30 μm
Hyphae branch @	45°	90°
Morphology	Dichotomous	Bulbous lateral protrusion



References

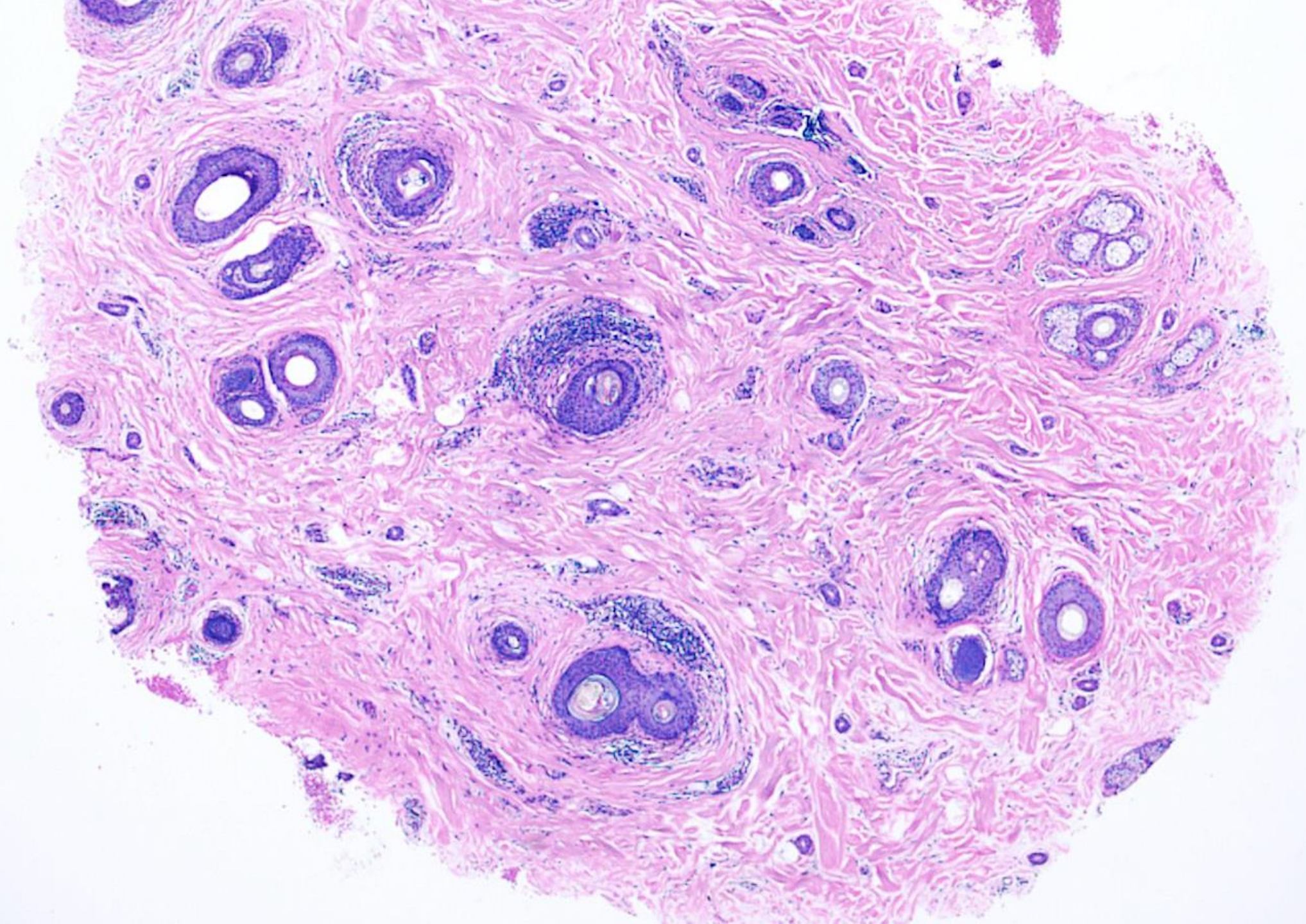
- + *Dermatopathology* (Barnhill)
- + *McKee's pathology of the skin*
- + <https://digitalskinpathology.com/>
- + Dadras archives

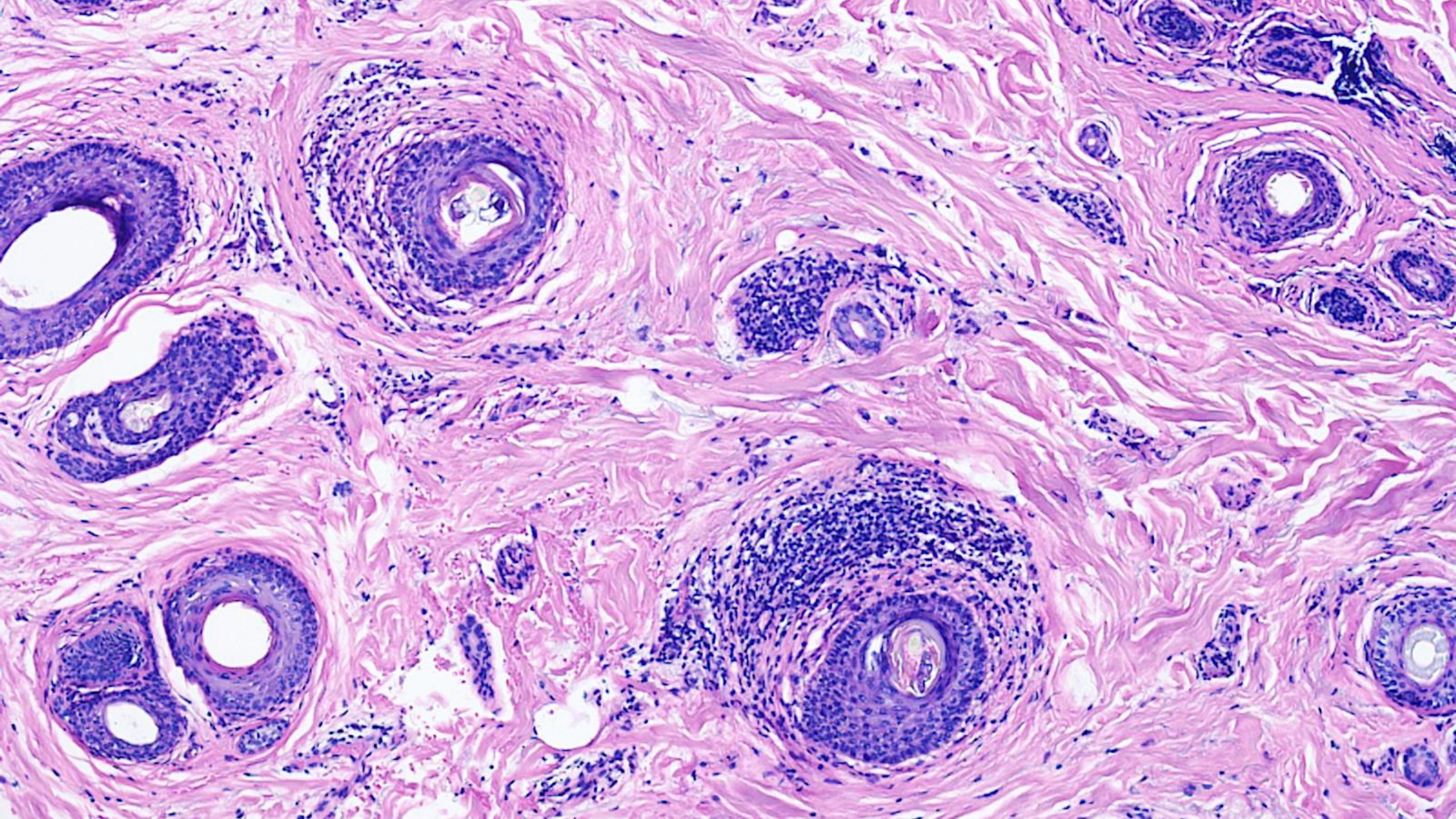


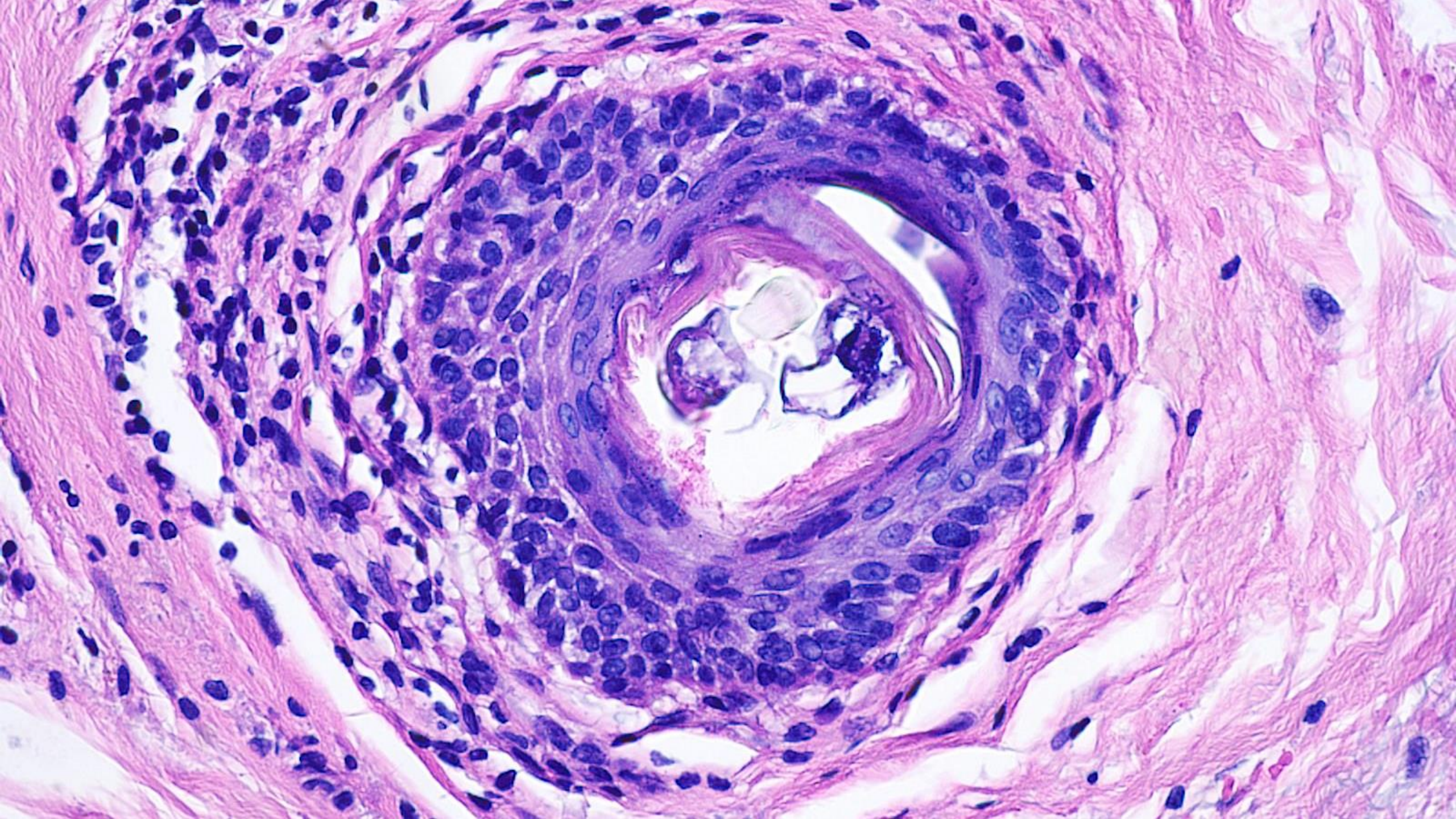


QUIZ: FUNGAL INFECTIONS

Soheil S. Dadras MD-PhD





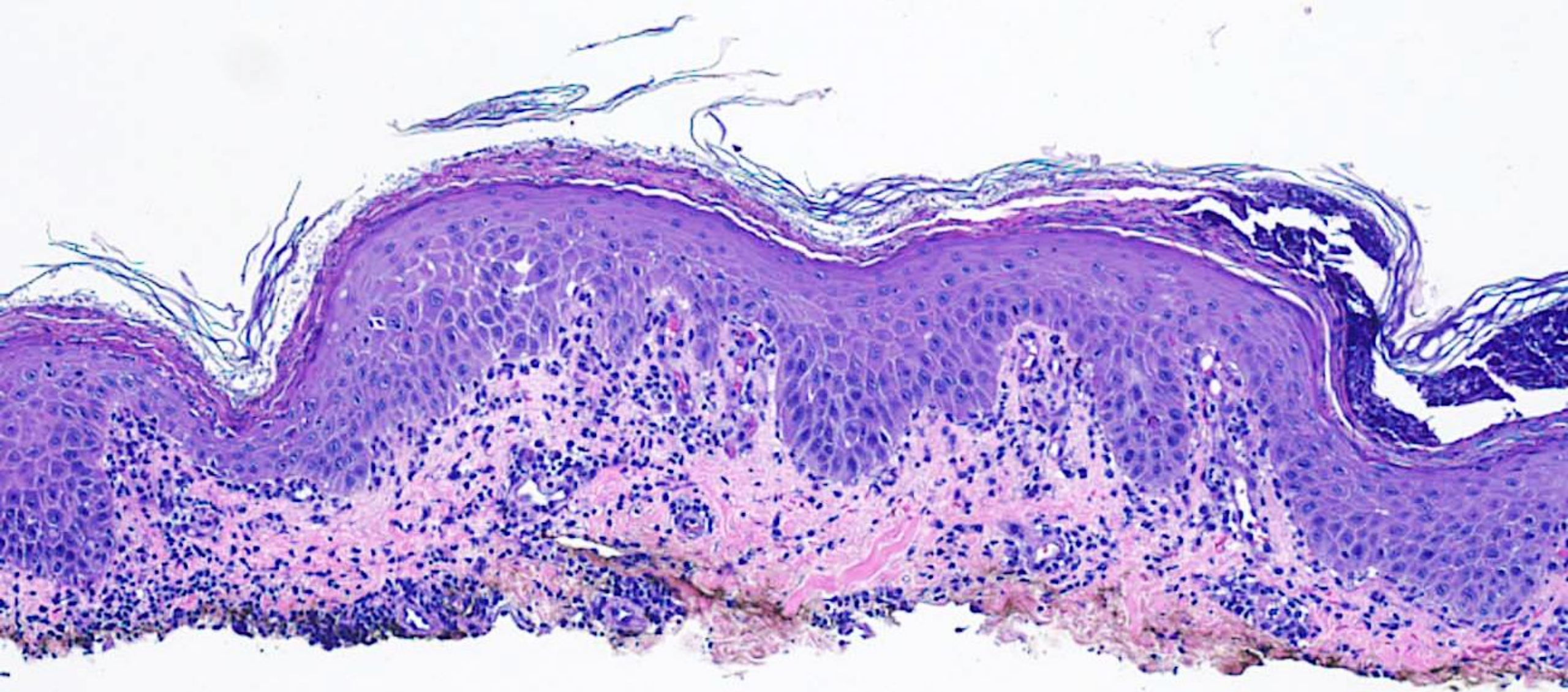


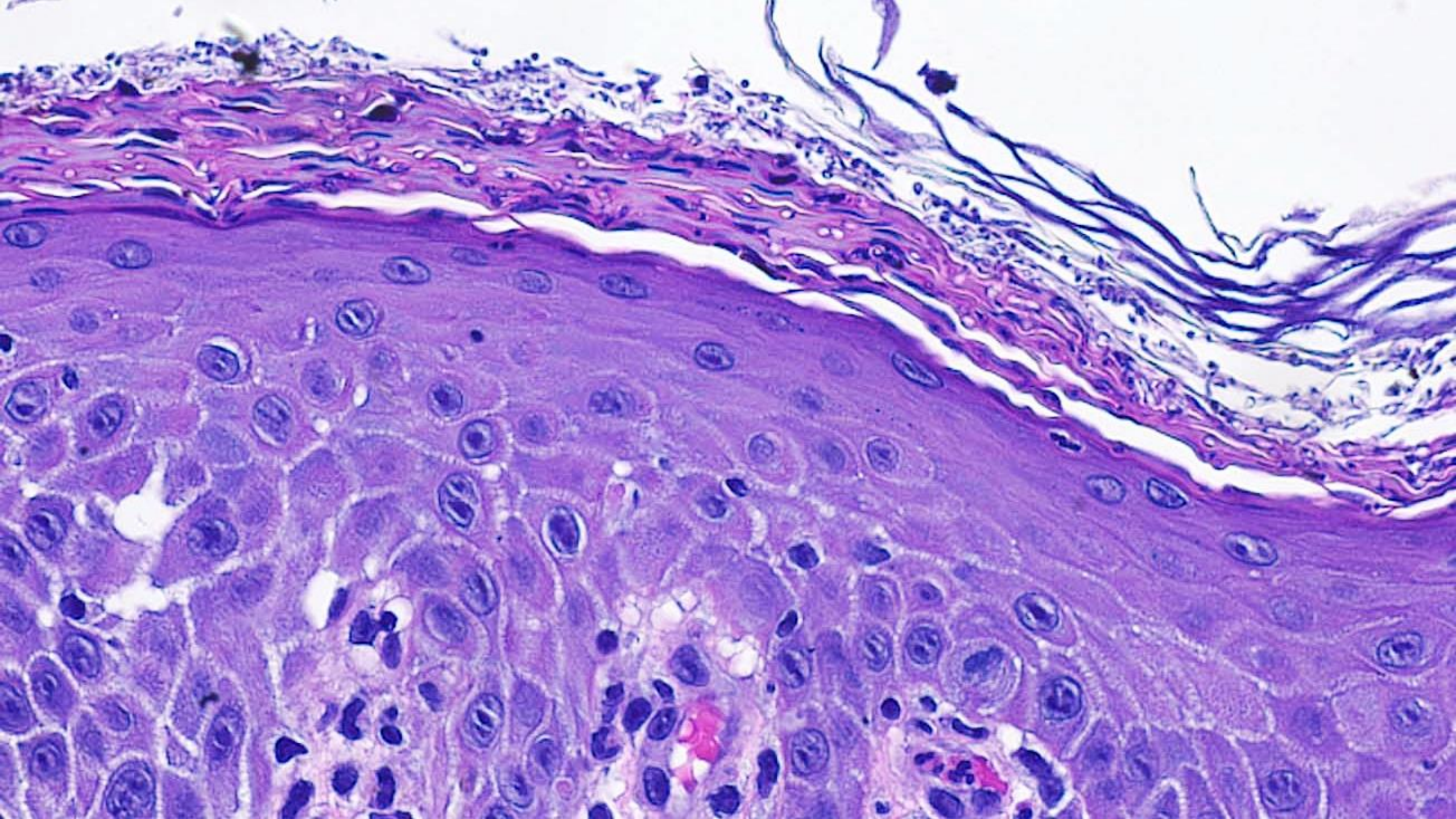
Case 1. 59F Scalp, non-scarring alopecia; androgenetic alopecia vs. chronic telogen effluvium. What is your diagnosis?

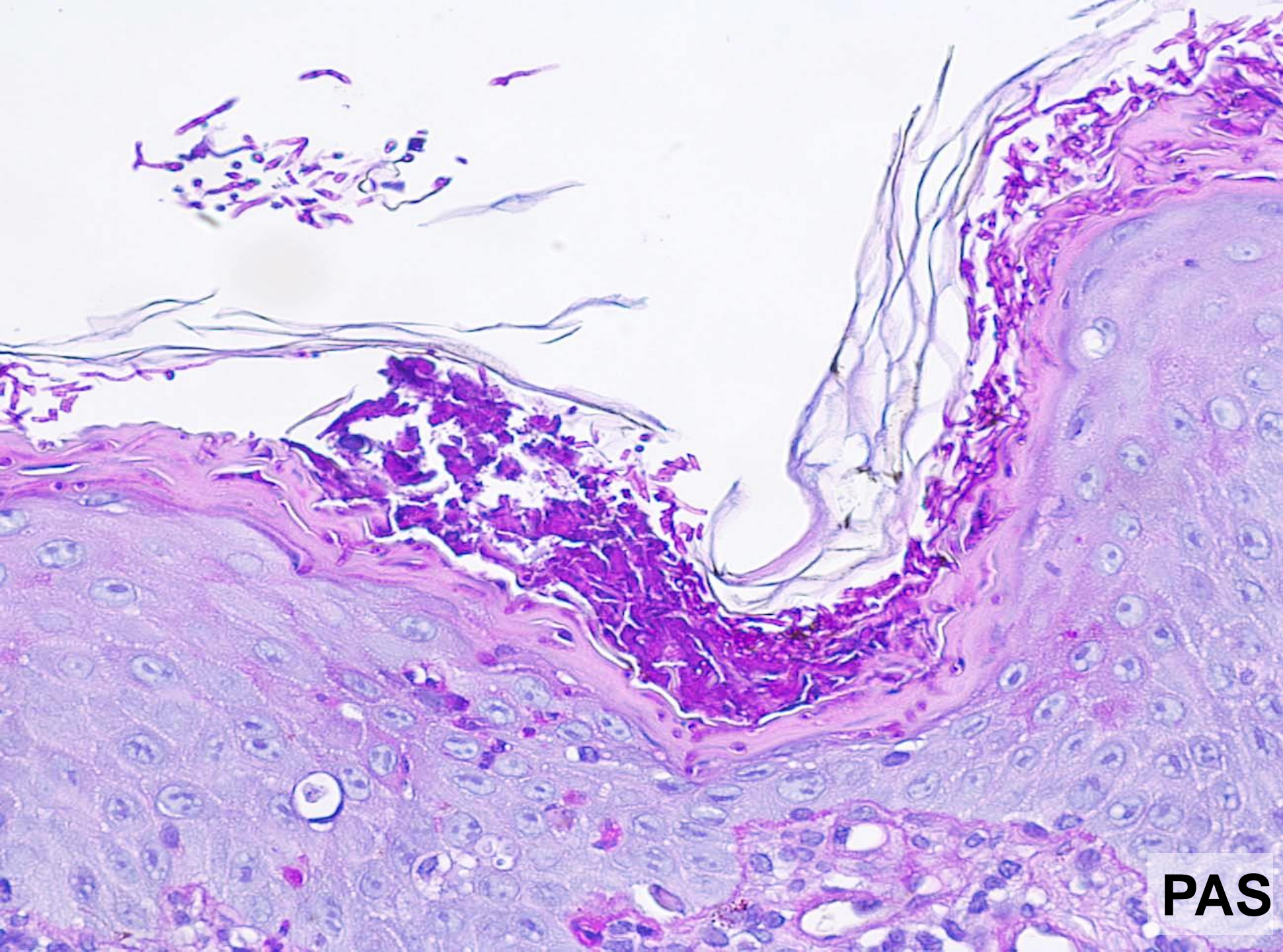
- A. Androgenetic alopecia
- B. Telogen effluvium
- C. Lichen planopilaris
- D. Androgenetic alopecia and *Demodex* folliculitis
- E. *Demodex* folliculitis of the scalp (rosacea)

Case 1. 59F Scalp, non-scarring alopecia, androgenetic alopecia vs. chronic telogen effluvium. What is your diagnosis?

+D. Androgenetic alopecia and *Demodex* folliculitis







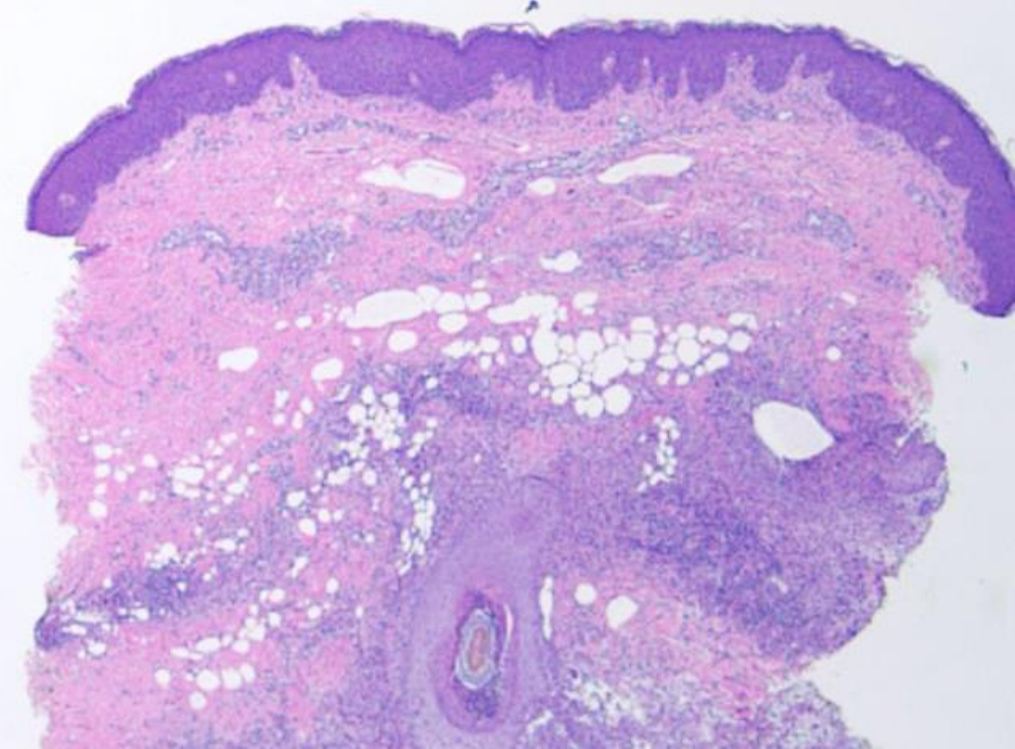
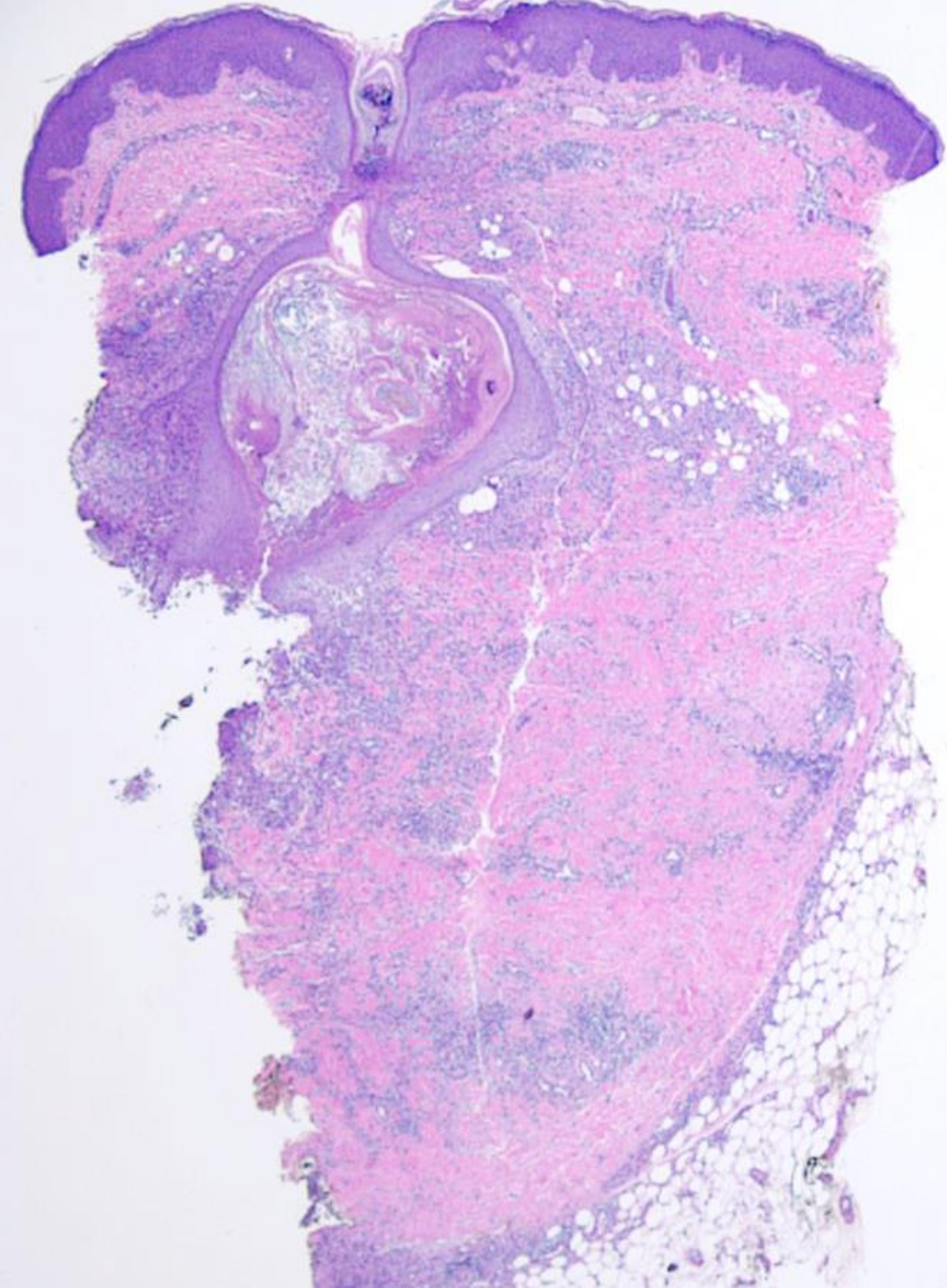
PAS

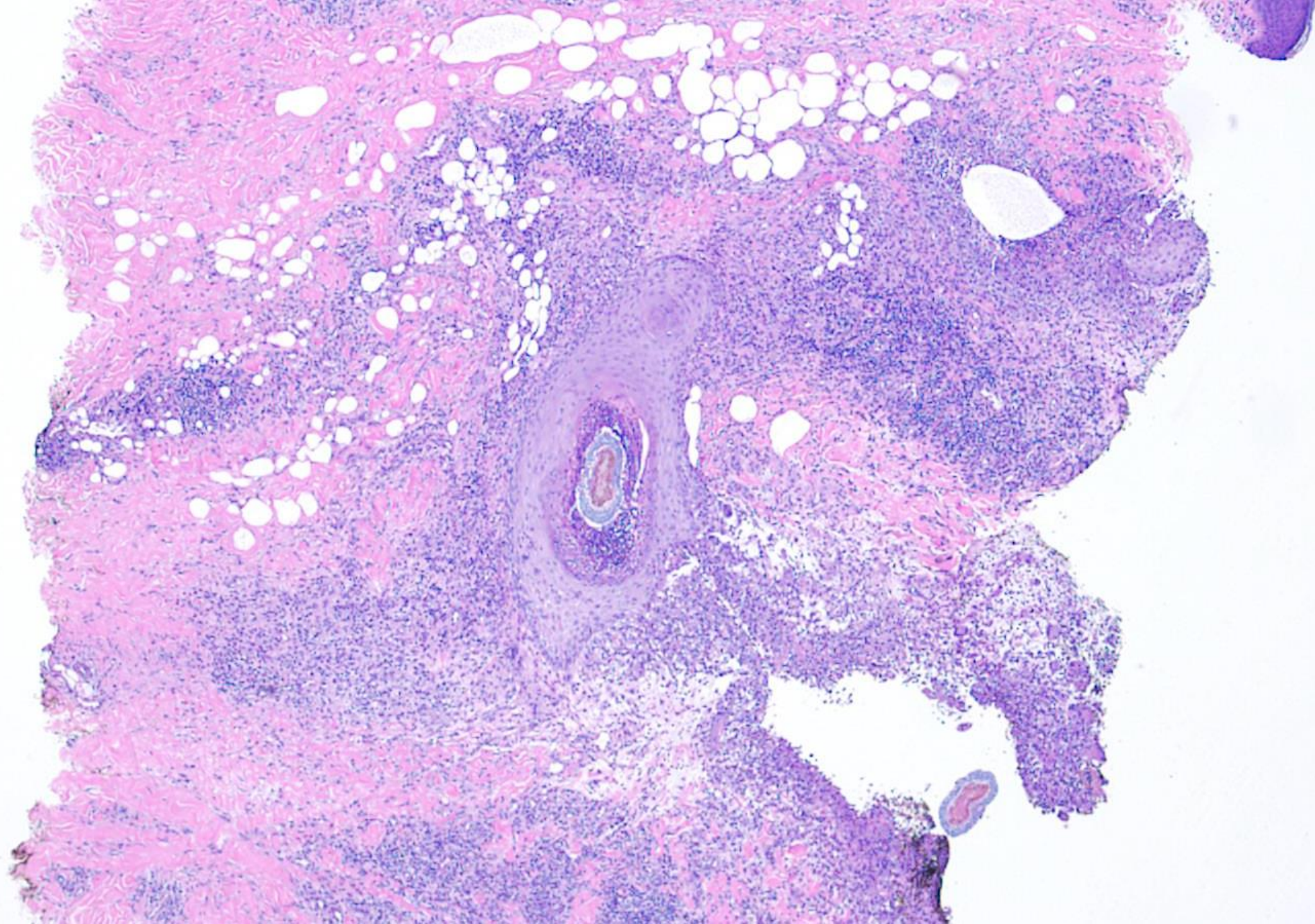
Case 2.47M, left posterior thigh; itchy erythematous rash with central clearing and peripheral scaling. What is your diagnosis?

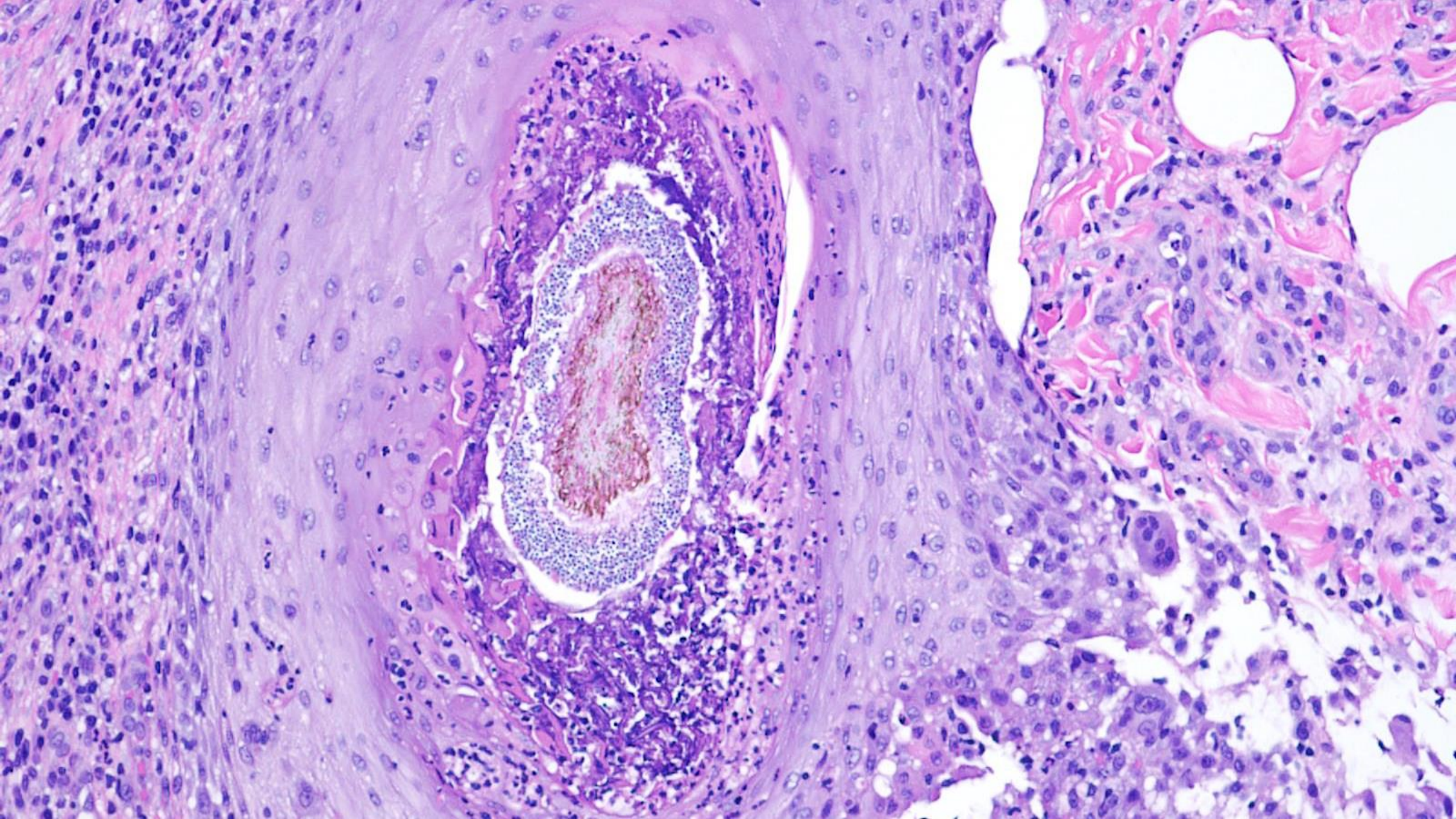
- A. Atopic dermatitis
- B. Allergic contact dermatitis
- C. *Tinea cruris*
- D. *Tinea folliculitis*
- E. Cutaneous mucormycosis

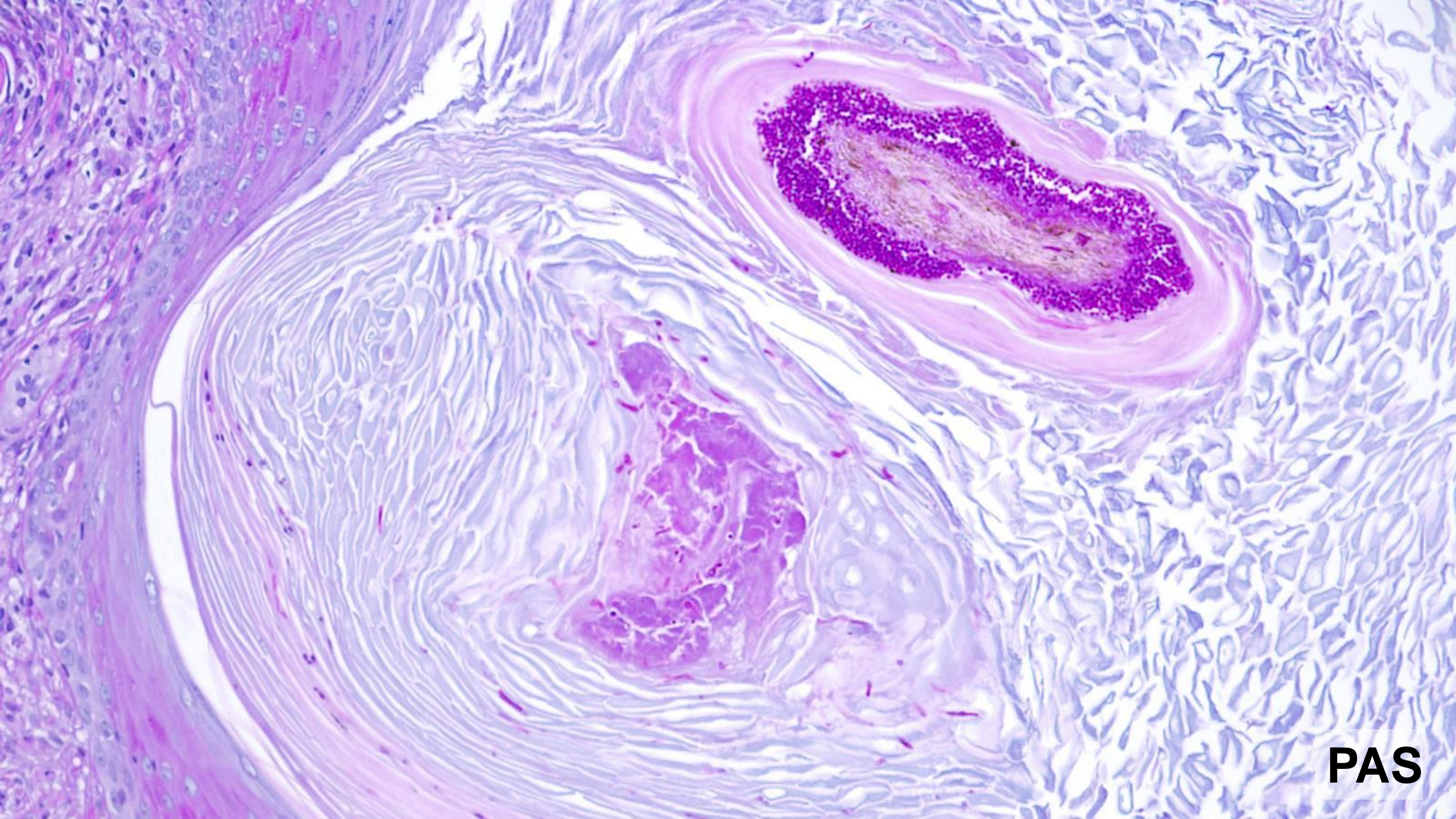
Case 2.47M, left posterior thigh; itchy erythematous rash with central clearing and peripheral scaling. What is your diagnosis?

+C. *Tinea cruris*





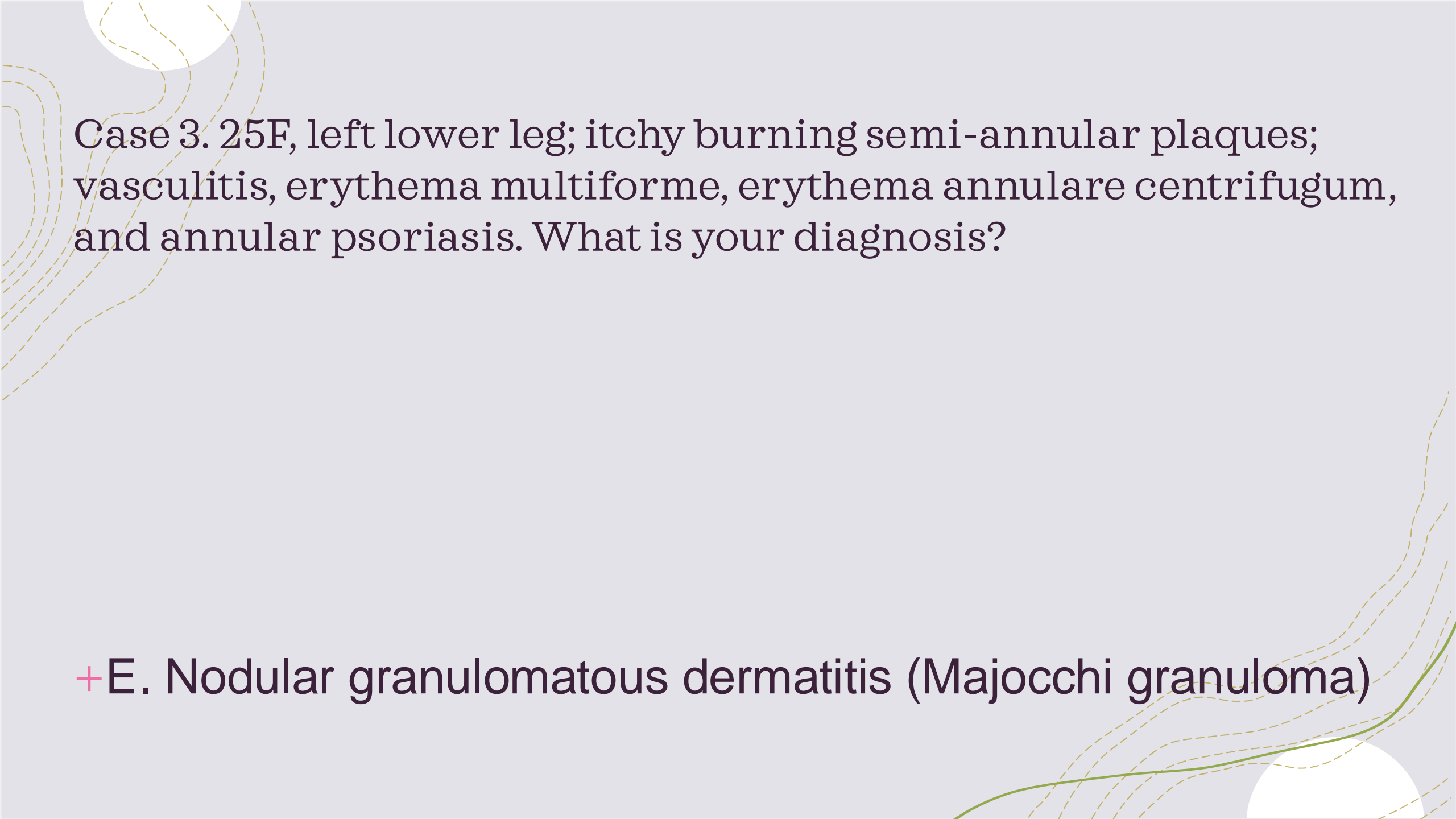




PAS

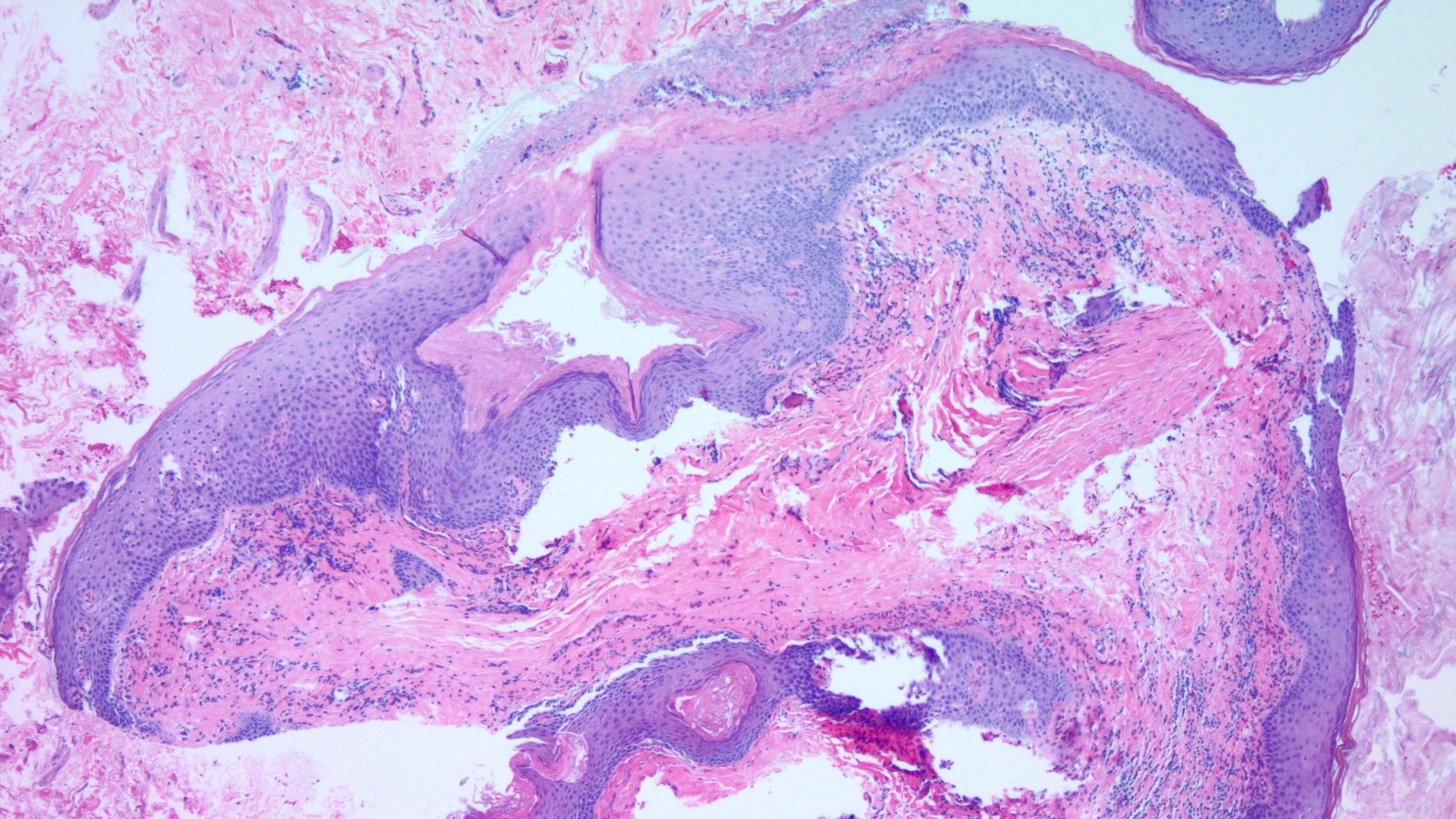
Case 3. 25F, left lower leg; itchy burning semi-annular plaques; vasculitis, erythema multiforme, erythema annulare centrifugum, and annular psoriasis. What is your diagnosis?

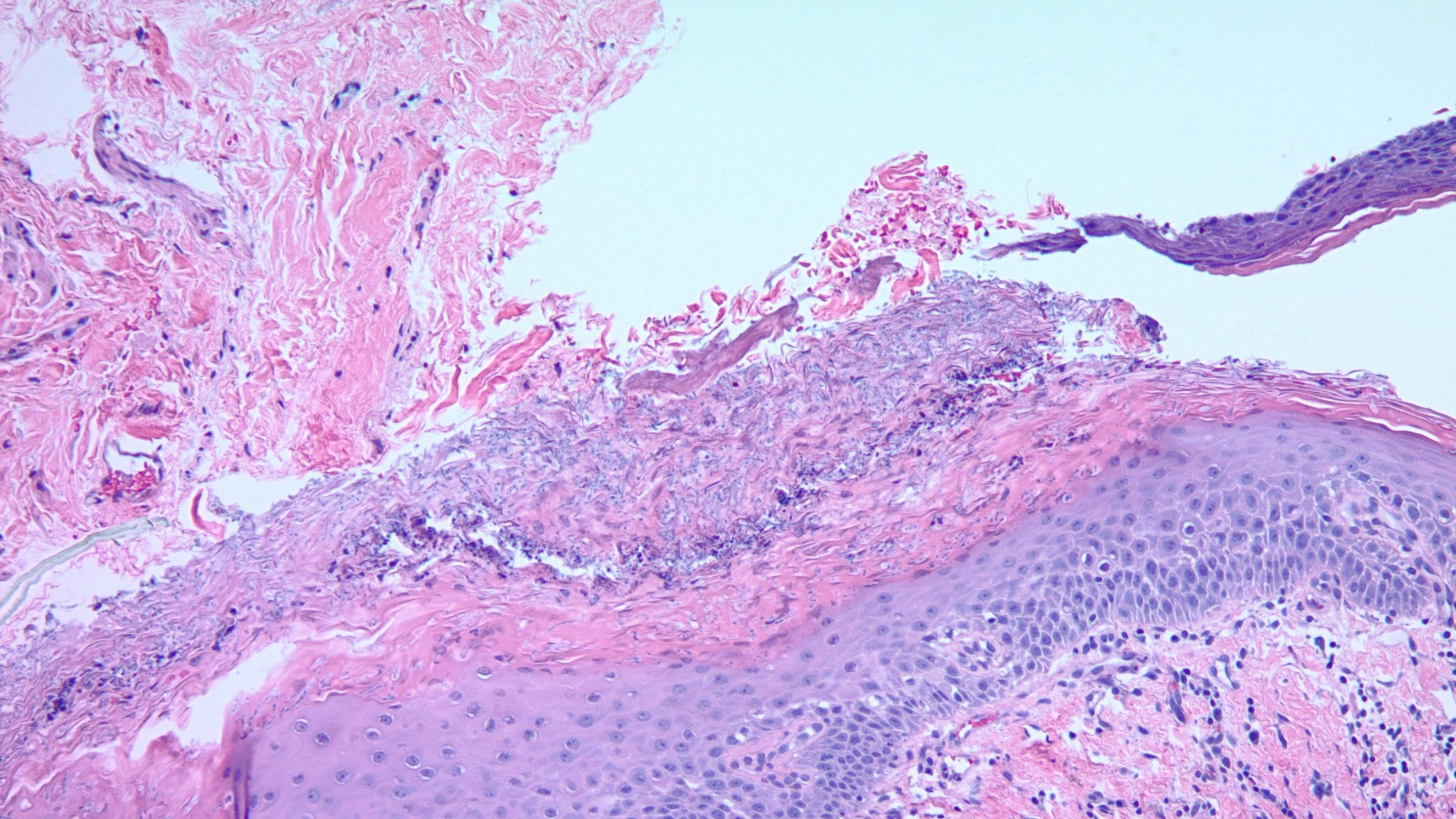
- A. Suppurative folliculitis
- B. *Tinea cruris*
- C. *Tinea* folliculitis
- D. Cutaneous mucormycosis
- E. Nodular granulomatous dermatitis (Majocchi granuloma)

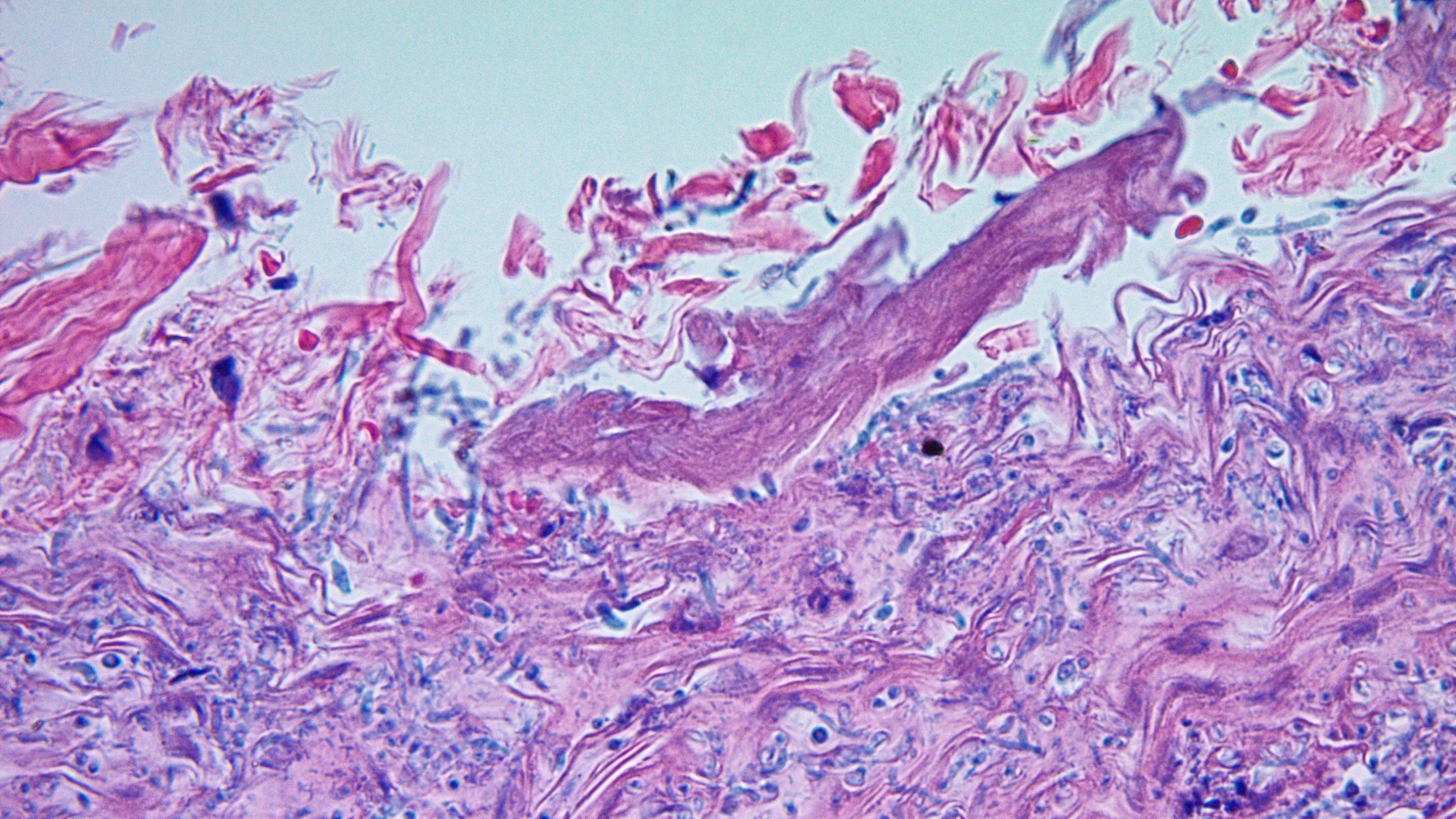


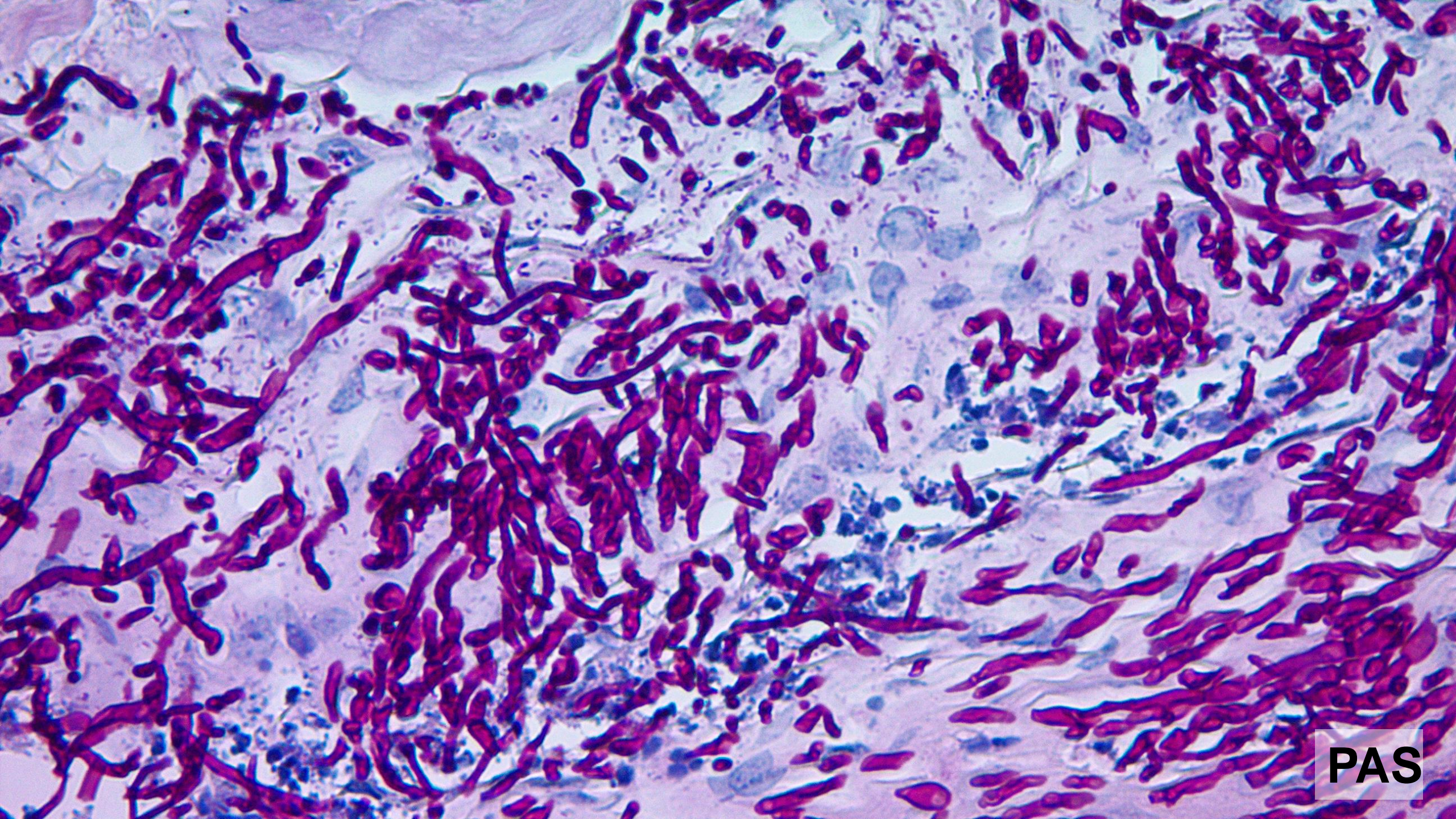
Case 3. 25F, left lower leg; itchy burning semi-annular plaques; vasculitis, erythema multiforme, erythema annulare centrifugum, and annular psoriasis. What is your diagnosis?

+E. Nodular granulomatous dermatitis (Majocchi granuloma)









PAS



Case 4. 59F, left vulva; lump. What is your diagnosis?

- A. Epidermal inclusion cyst, fragmented
- B. *Tinea cruris*
- C. *Tinea* folliculitis
- D. *Tinea genitalis* and fragments of epidermal inclusion cyst
- E. Cutaneous mucormycosis



Case 4. 59F, left vulva; lump. What is your diagnosis?

+D. *Tinea genitalis* and fragments of epidermal inclusion cyst