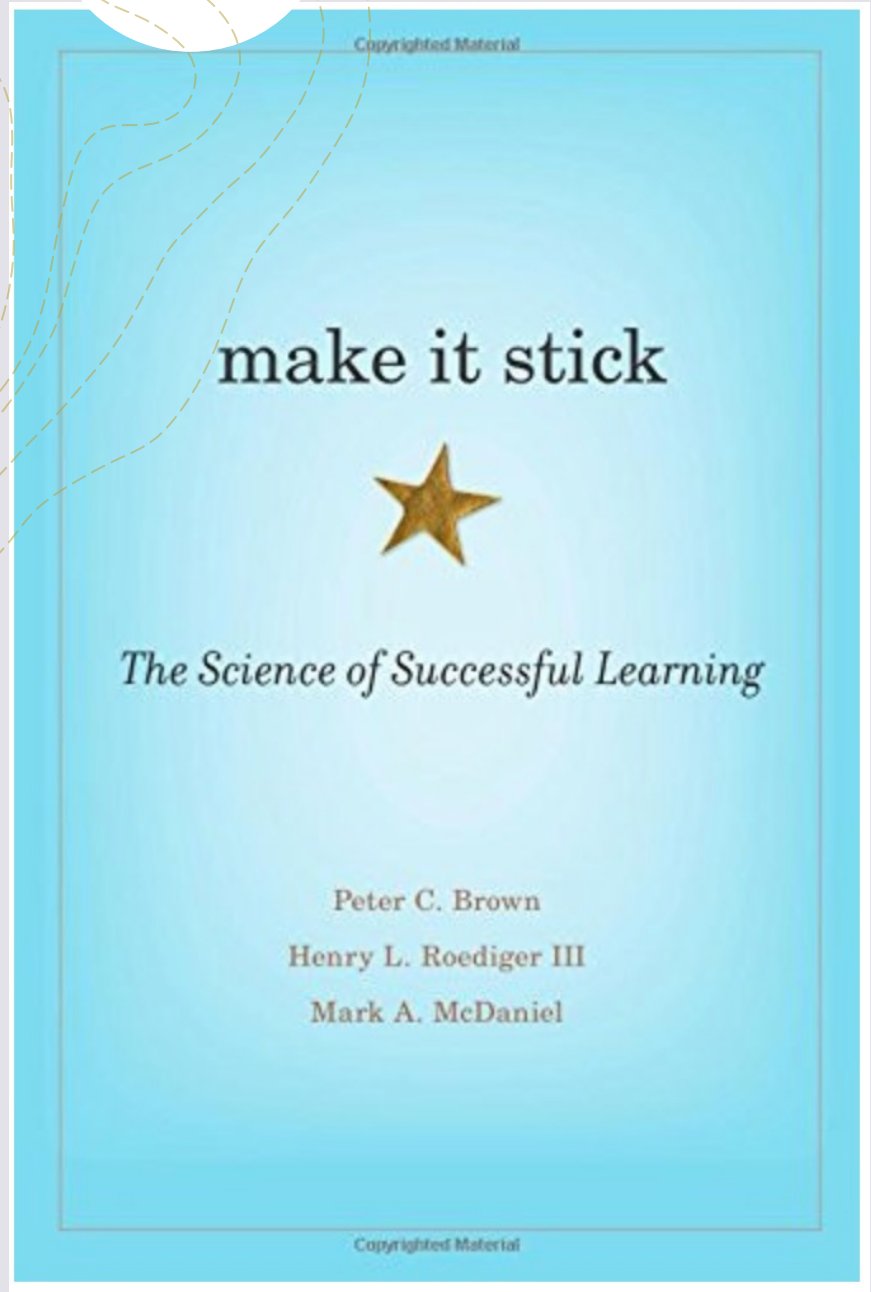
Fungal Infections

Soheil S. Dadras MD-PhD



How to learn dermatopathology more effectively

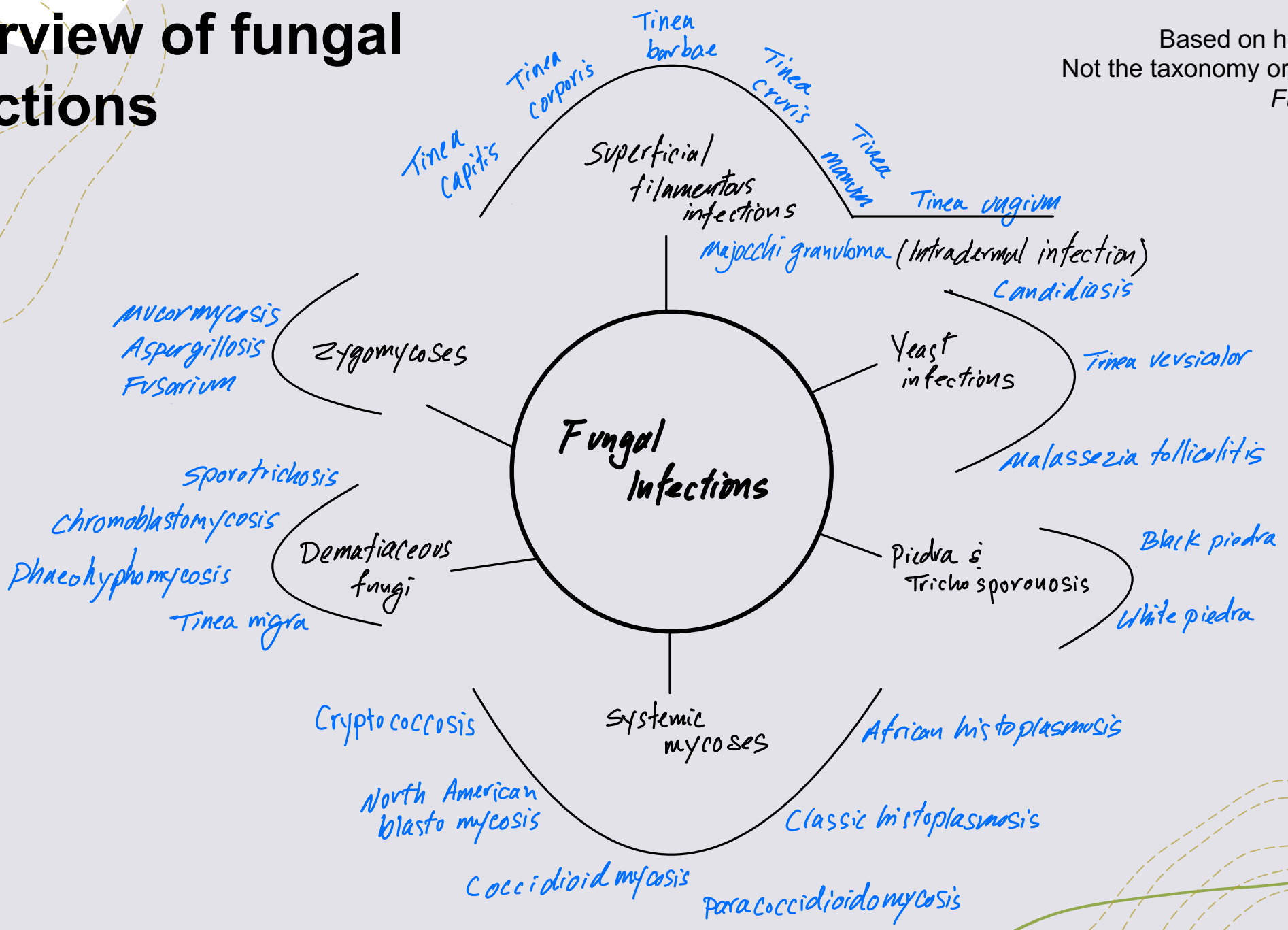
- Many are life-long learners (hopefully)
- Learning should be effortful (painful), not too easy
- Rereading, multiple color highlights is wasteful (too easy)
- Mnemonic devices (plus/minus)
- Avoid illusion of mastery
- Retrieval practice (not rereading), testing is a good thing
- Quizzes and tests (power of testing as a learning tool)
- https://www.retrievalpractice.org/make-it-stick

Going forward, incorporating:

1. Dermatopathology mind mapping (organize thoughts and learning points)
2. Dermatopathology quizzes

Overview of fungal infections

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

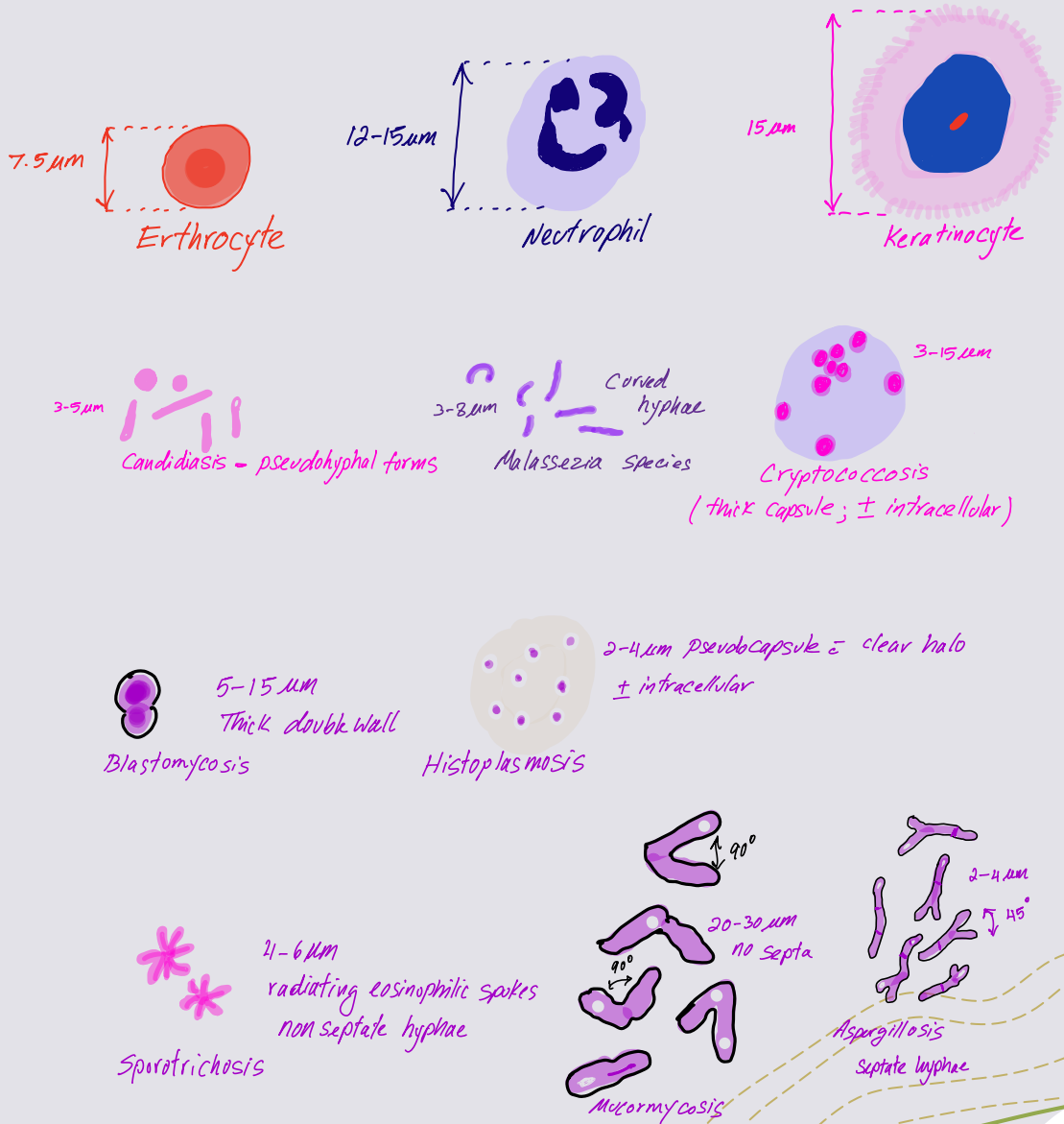


Range of histologic tissue reaction patterns to fungal infections

- 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



DIGITAL SKIN PATHOLOGY (DiSK)
Learn Histologic Diagnosis Case-By-Case

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 Chow [1], Li Mei Pang [2] 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.

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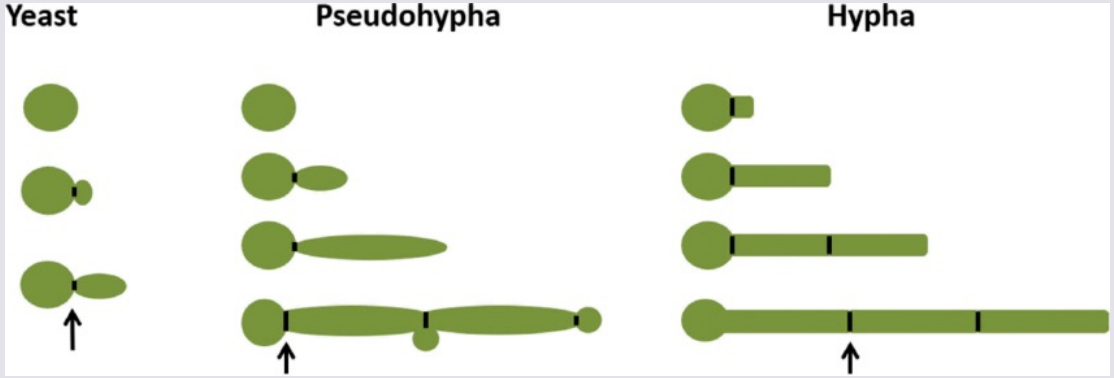
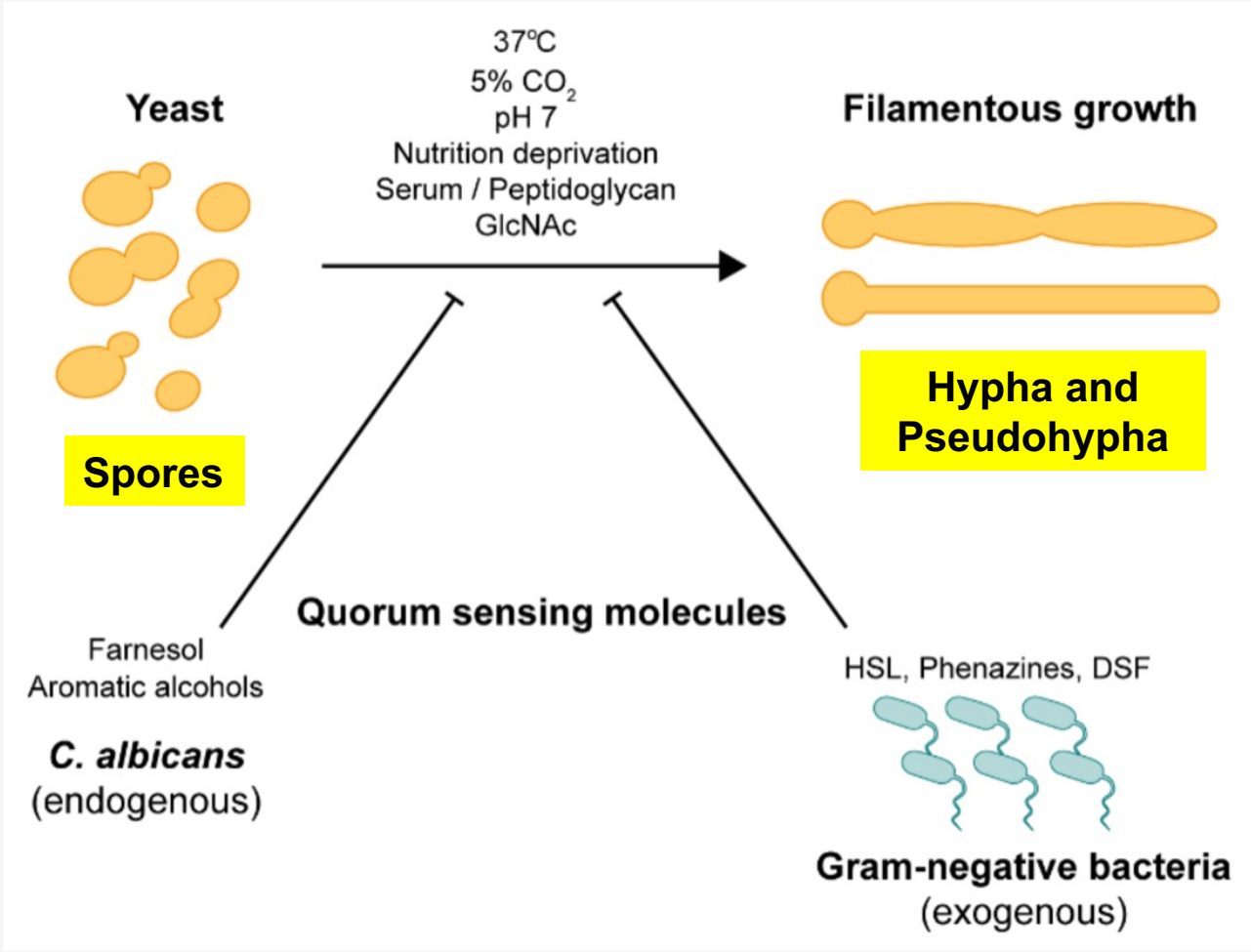
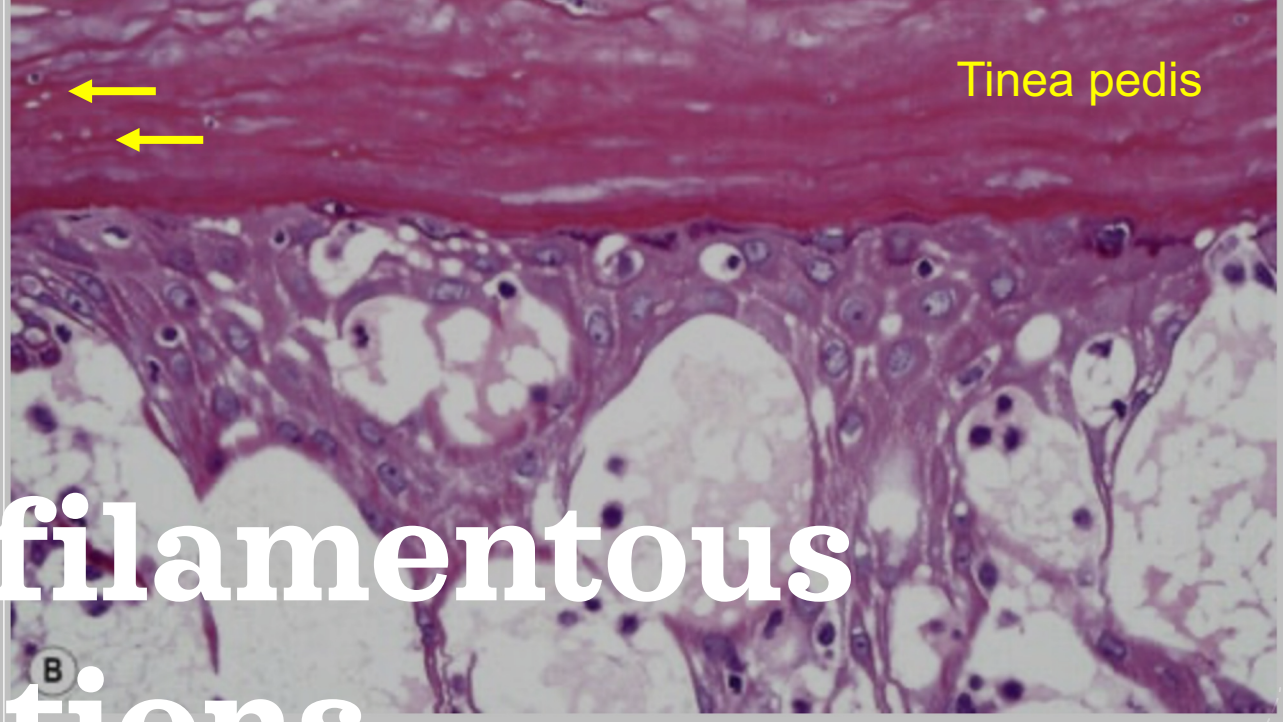


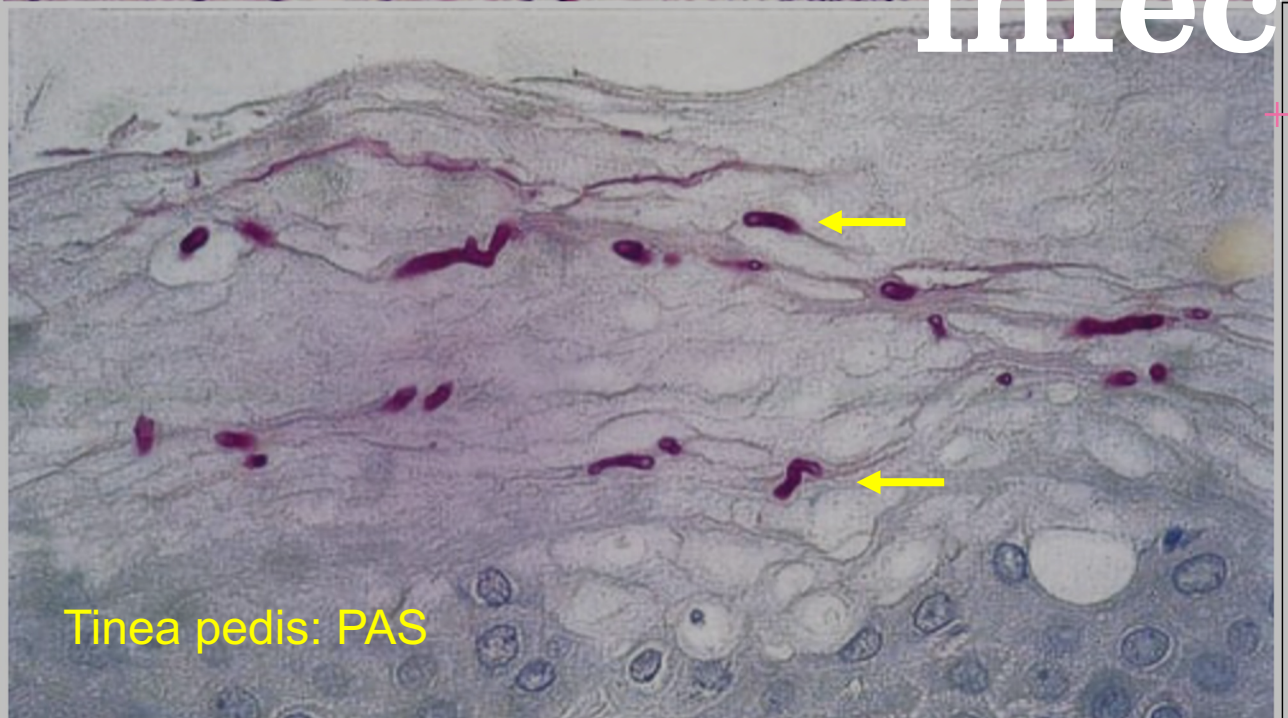
Black arrow indicate septin ring
The width of pseudohyphae cells are larger than hyphal cells

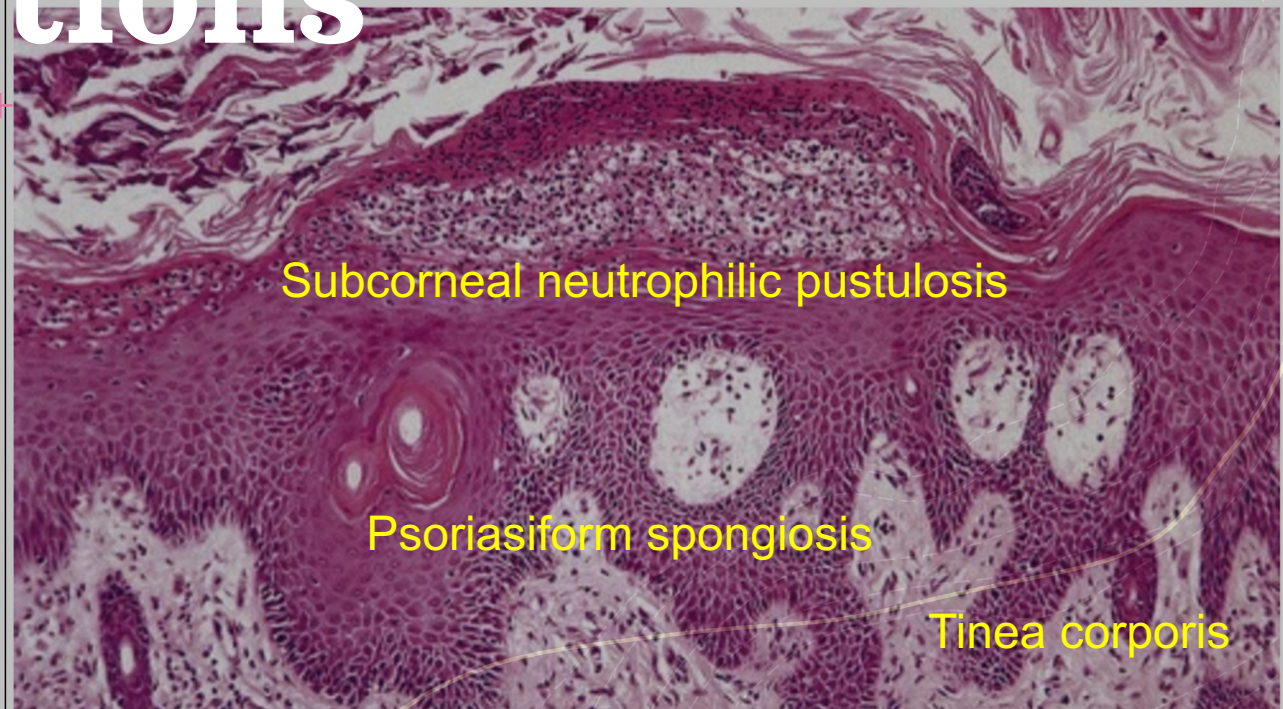
Figure 1. External hyphal-inducing signals. The yeast-to-hyphae transition in *C. albicans* can be triggered by various environmental cues such as high temperature (37 °C), high CO_2 concentration (~5%), pH 7, nutrition deprivation, serum, peptidoglycan, *N*-acetylglucosamine, and inhibited by quorum-sensing molecules from endogenous and exogenous sources.



Superficial filamentous infections

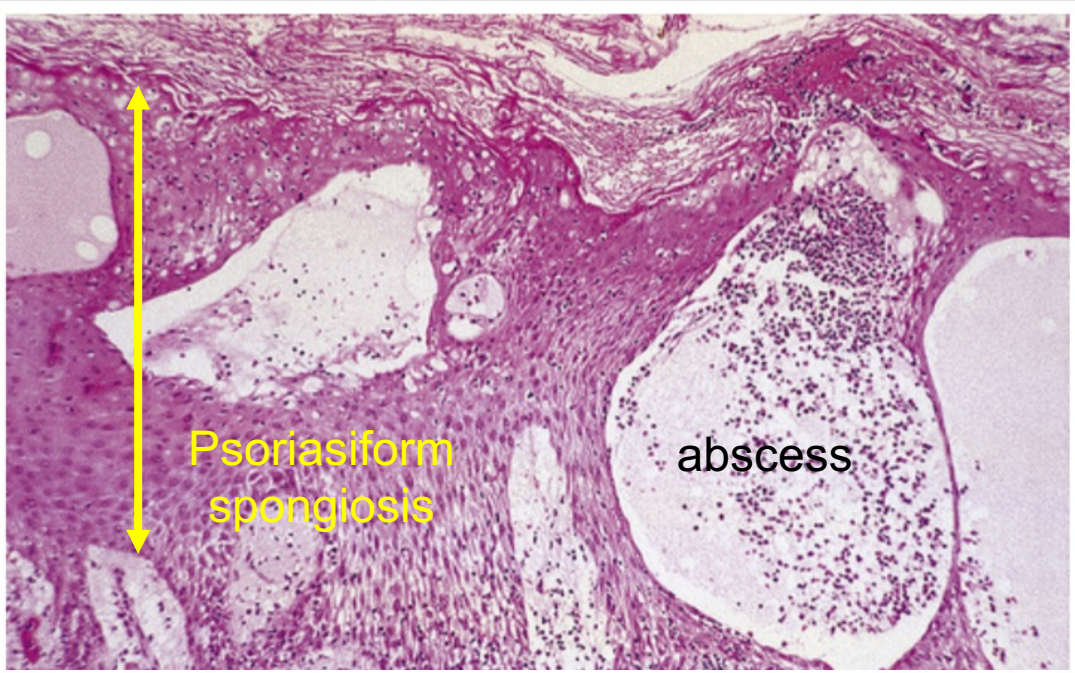


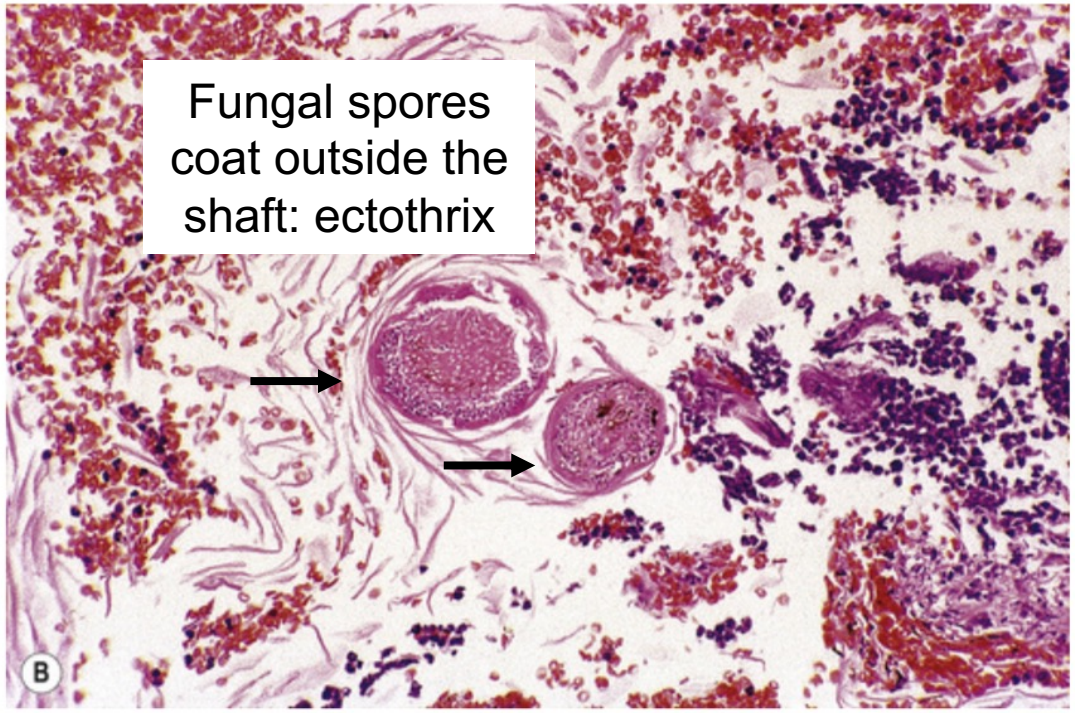




Tinea capitis

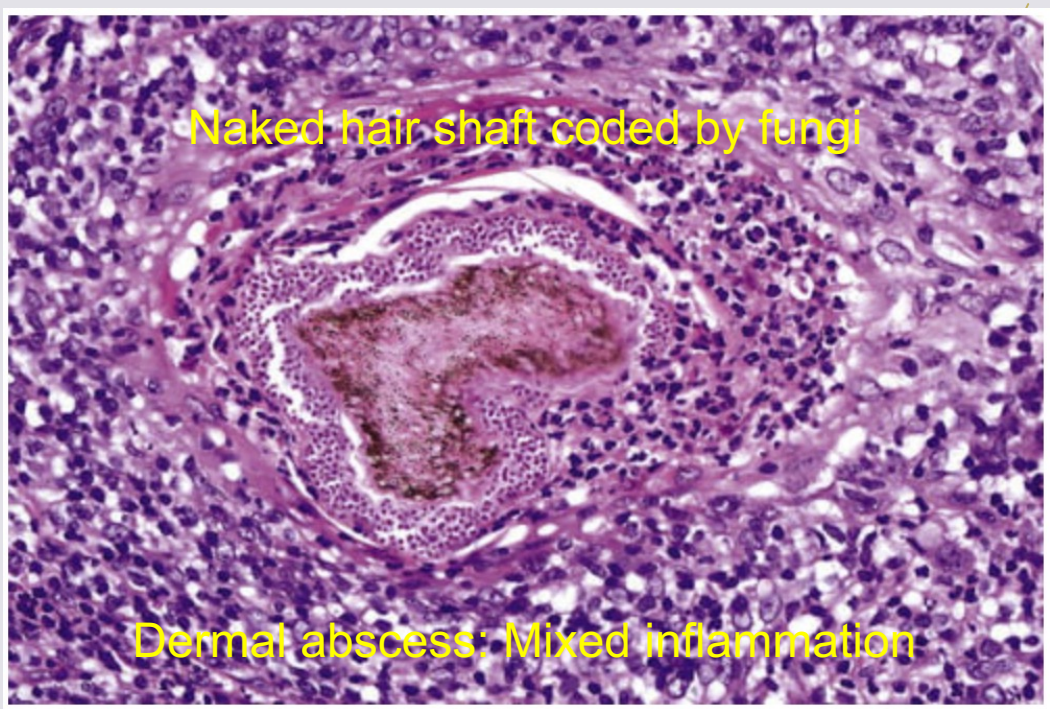
- *Trichophyton, Microsporum*
- Infections:
  - Ectotrhix: small or large spore
  - Endothrix: large spore
  - Begins with hyphal invasion of hair follicles
  - May lead to kerion (boggy, pus-filled lesions)
- Matted hairs, crusting, alopecia





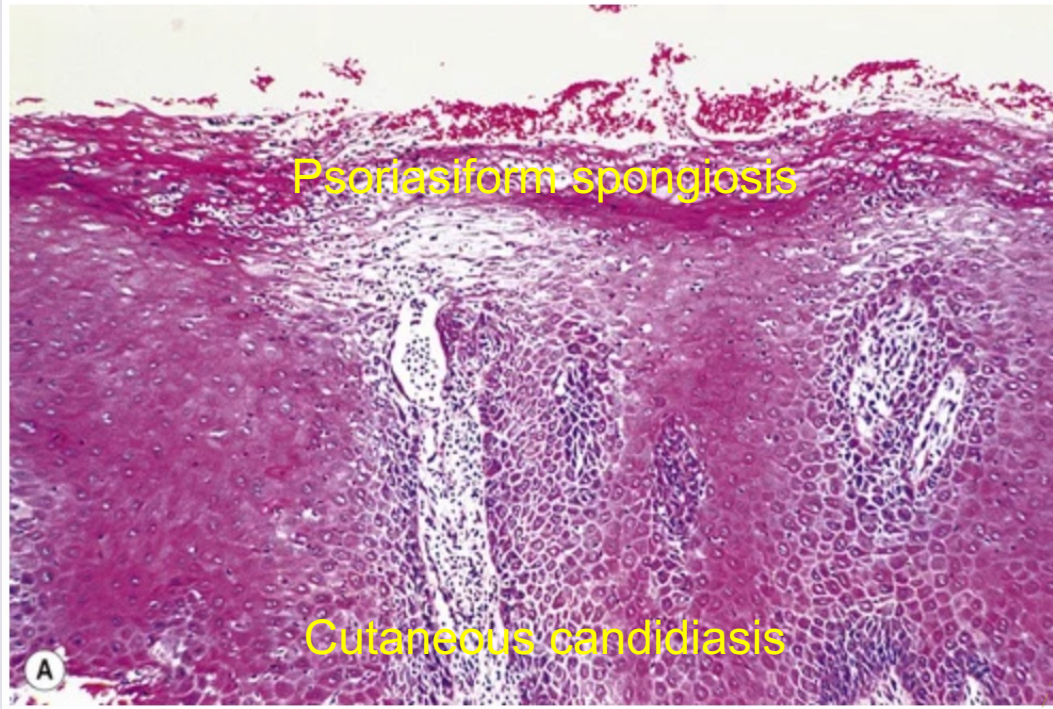
Nodular granulomatous dermatitis (Majocchi granuloma)

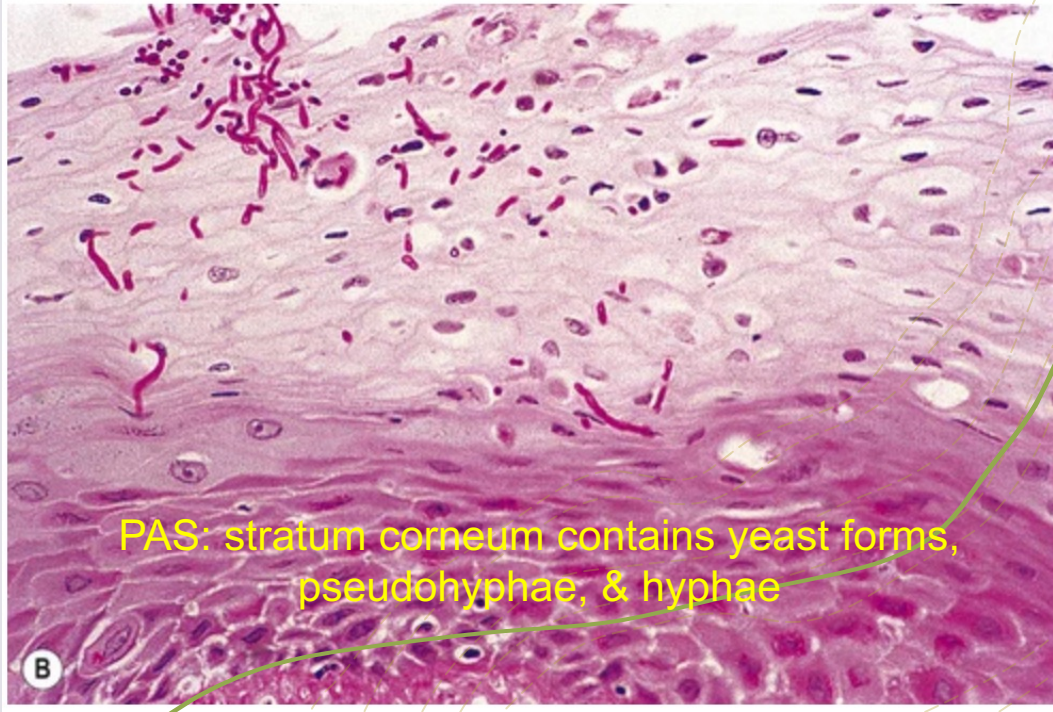
- Uncommon intradermal infection by dermatophytosis
- Presents clinically as granulomata, cellulitis, or plaques
- Anterior aspect of the legs
- Hyphae or spores
- Dermal neutrophilic abscess
- Organisms may be scanty or multiple
- Multiple step – leveled sections are important
- PAS, GMS



Mucocutaneous candidiasis

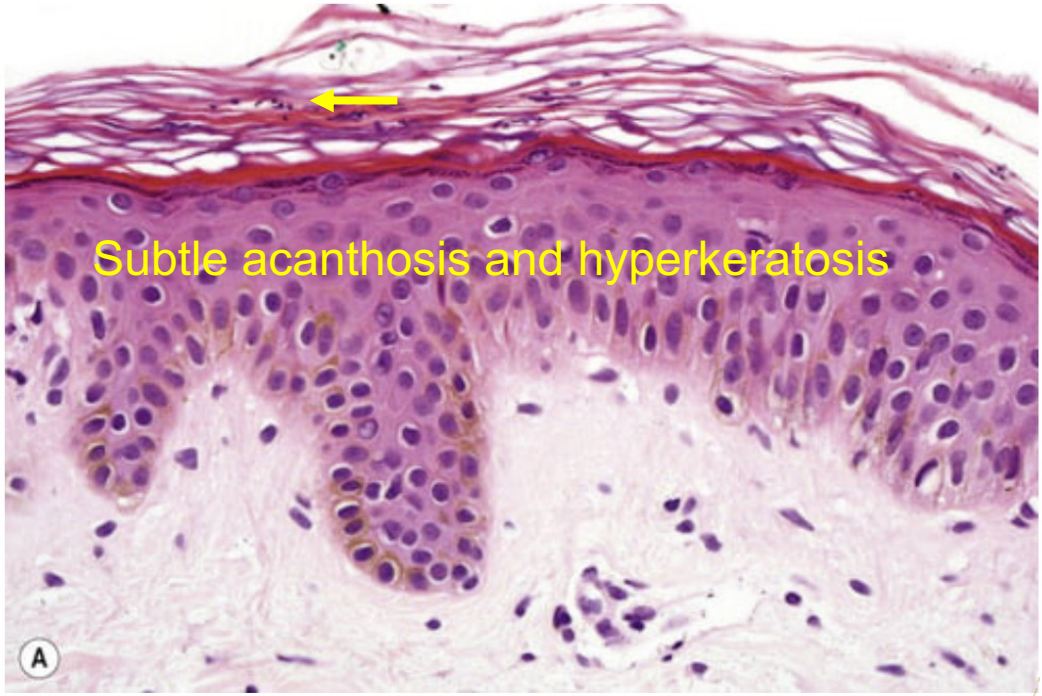
- Acute forms: more common in infants, elderly, pregnant, and diabetic patients
- Chronic forms: often associated with cell mediated immune deficiency
- Chronic atrophic candidiasis in denture wearers
- Disseminated: triad of fever, papular erythematous rash and myalgias in neutropenic patients (same 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

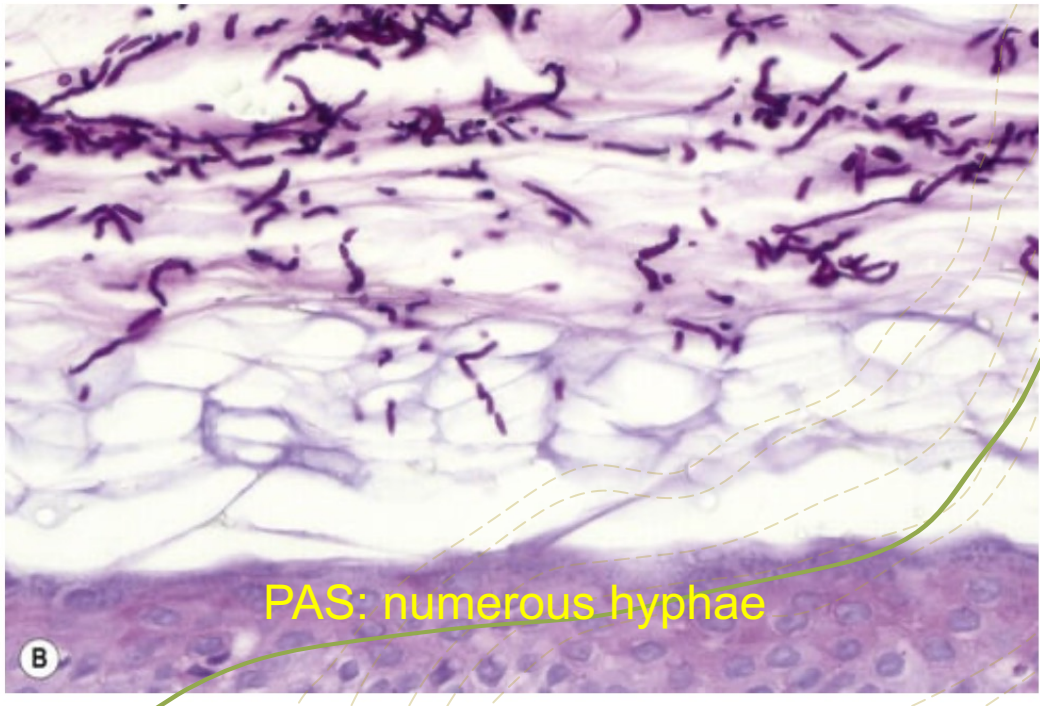




Tinea versicolor

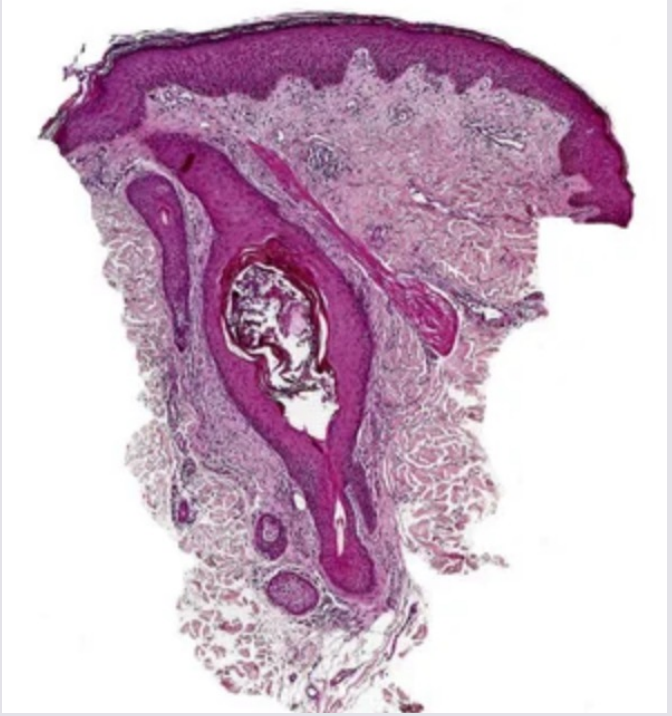
- Caused by *Malassezia*
- Warm months and tropics
- Early 20s in temperate zones
- Pale to brown, scaling macules over the upper trunk
- Differential diagnosis: tinea corporis, candidiasis, and spongiotic dermatitis



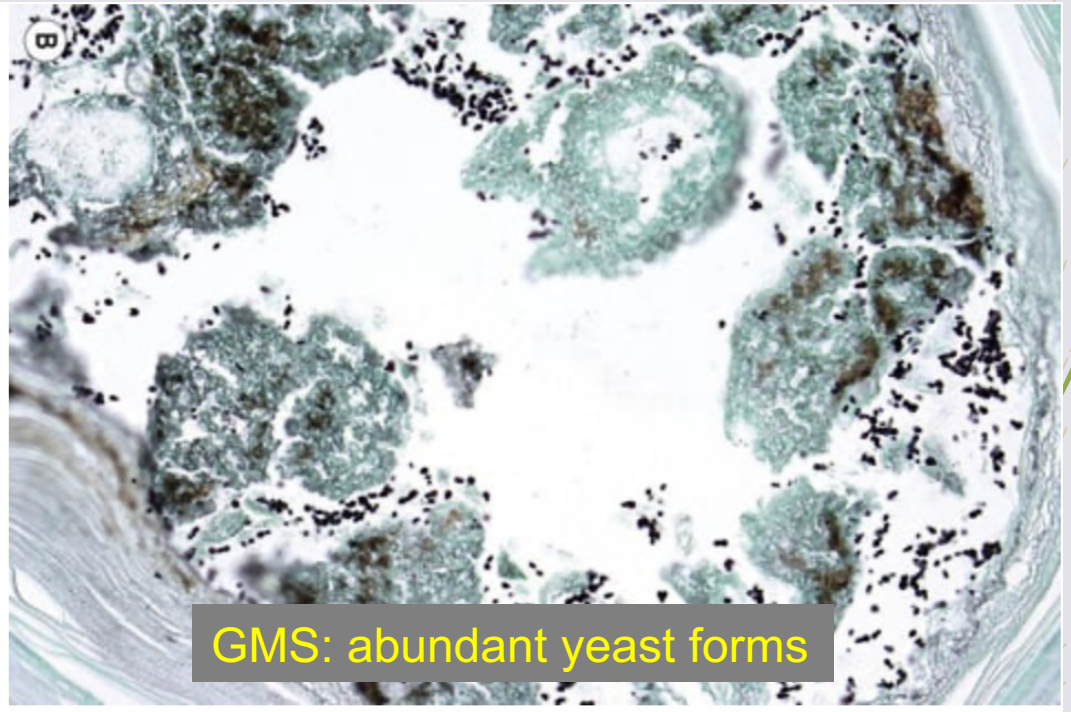


Malassezia (pityrosporum) folliculitis

- 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



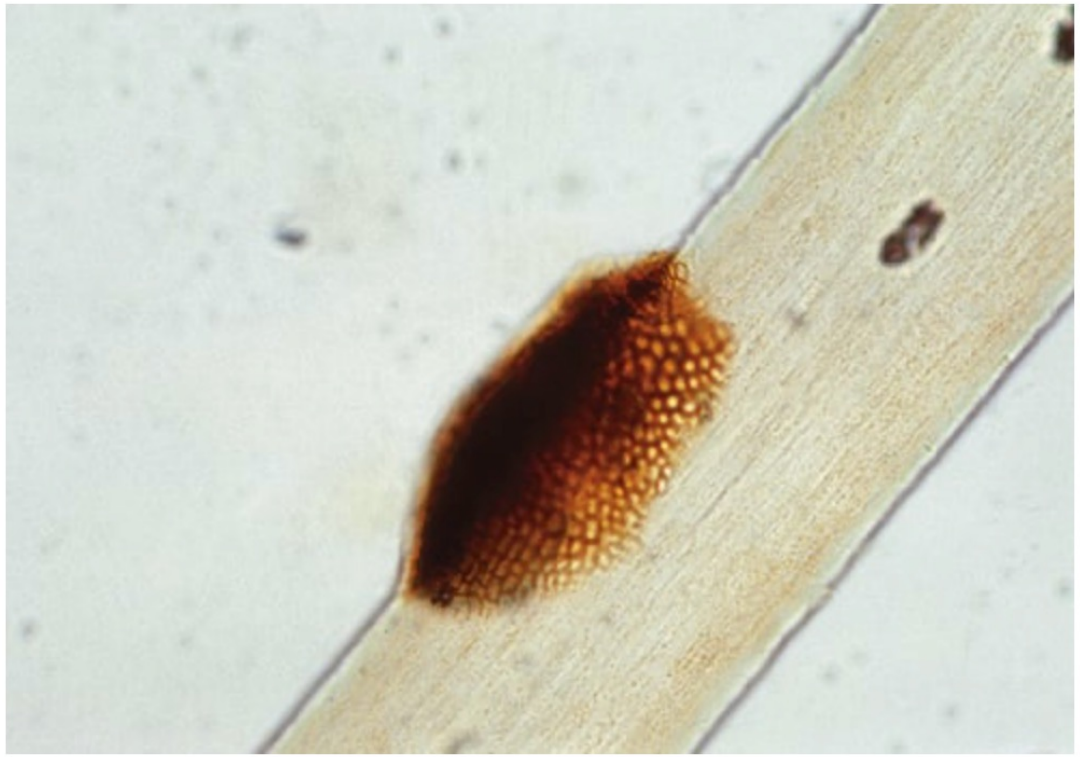
-Dilated follicle/
-Folliculitis
-Follicular plug
-Neutrophils, lymphocytes, histiocytes in and around follicles
-Foreign body reaction
-Pools of mucin



GMS: abundant yeast forms

Piedra (stone) and Trichospornosis

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

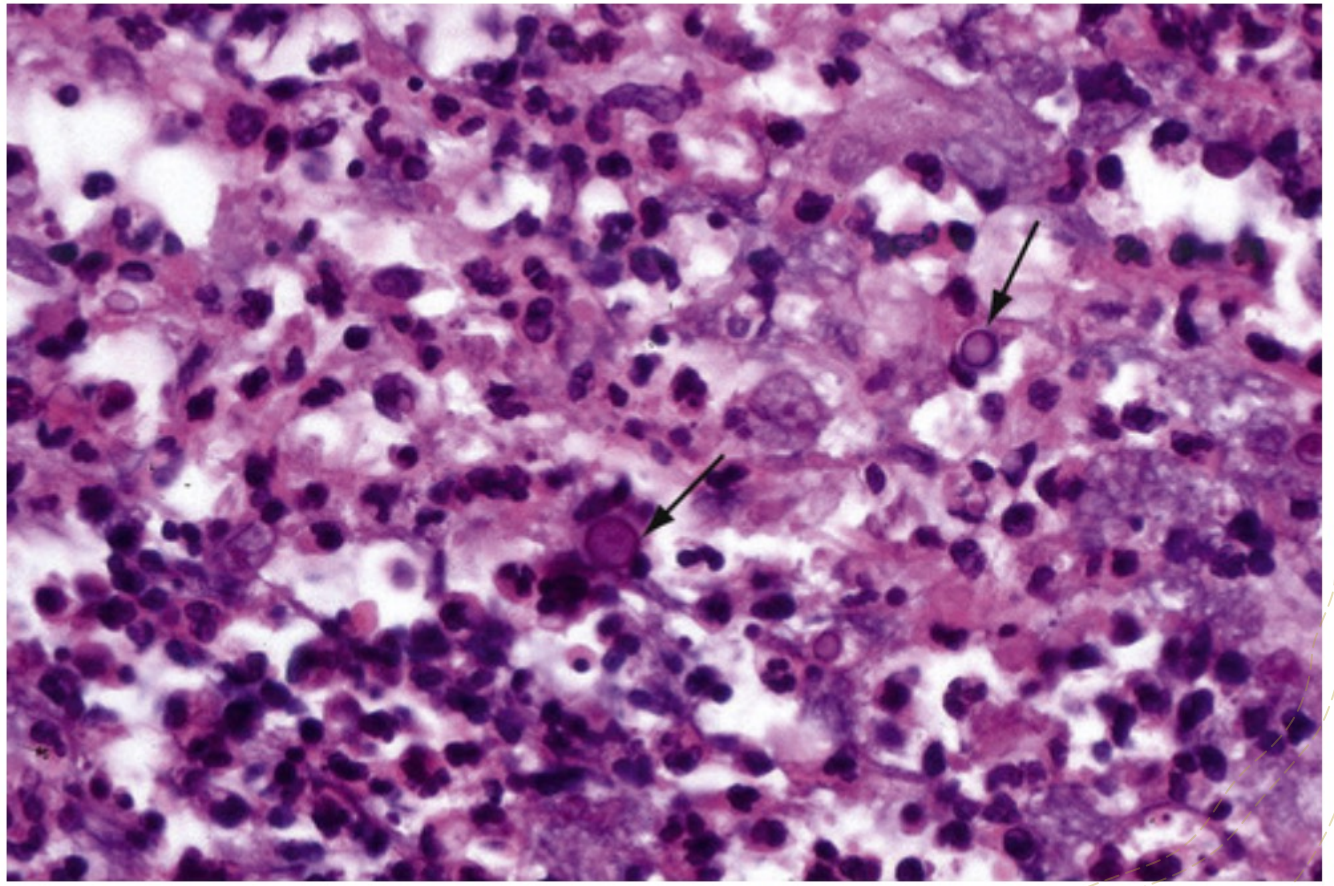


Black Piedra: brown nodule attached to hair shaft

Hair pull with KOH prep
Skin biopsy: normal

Systemic mycoses

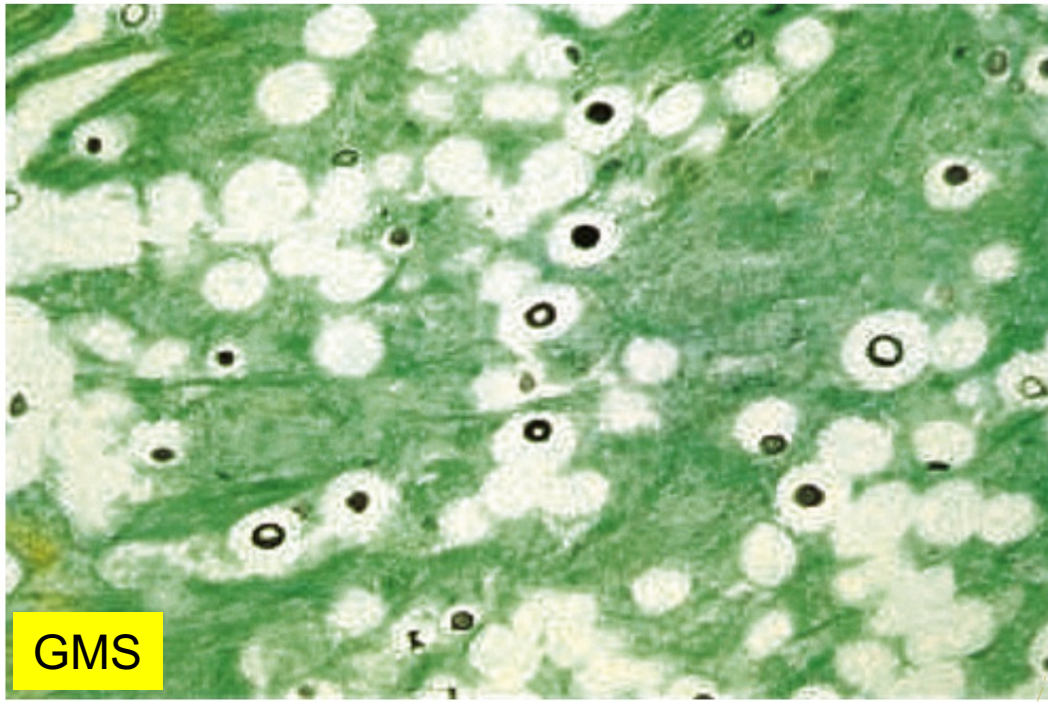
- The infection is respiratory
- Can spread due to failure of normal cell – mediated immune response or reactivation of dormant sites
- Mucocutaneous lesions can occur in 10% of patients with disseminated disease
- Skin lesions are essentially diagnostic of systemic disease because primary cutaneous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

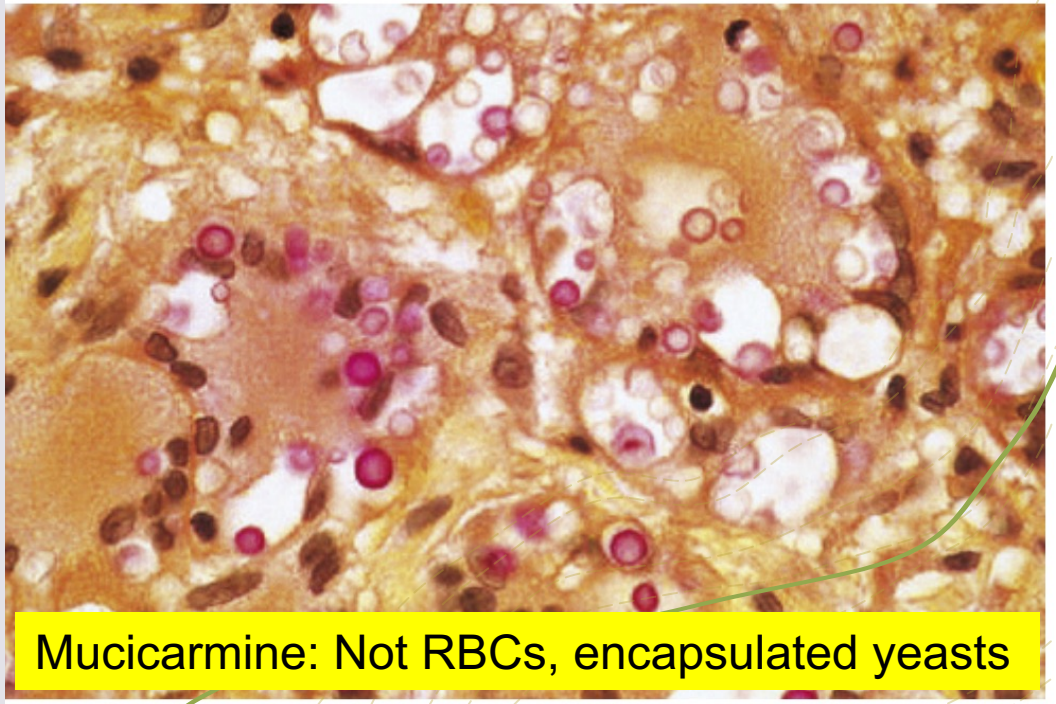


Cryptococcosis: Multiple yeast forms in a patient receiving corticosteroid therapy for lupus

Cryptococcosis

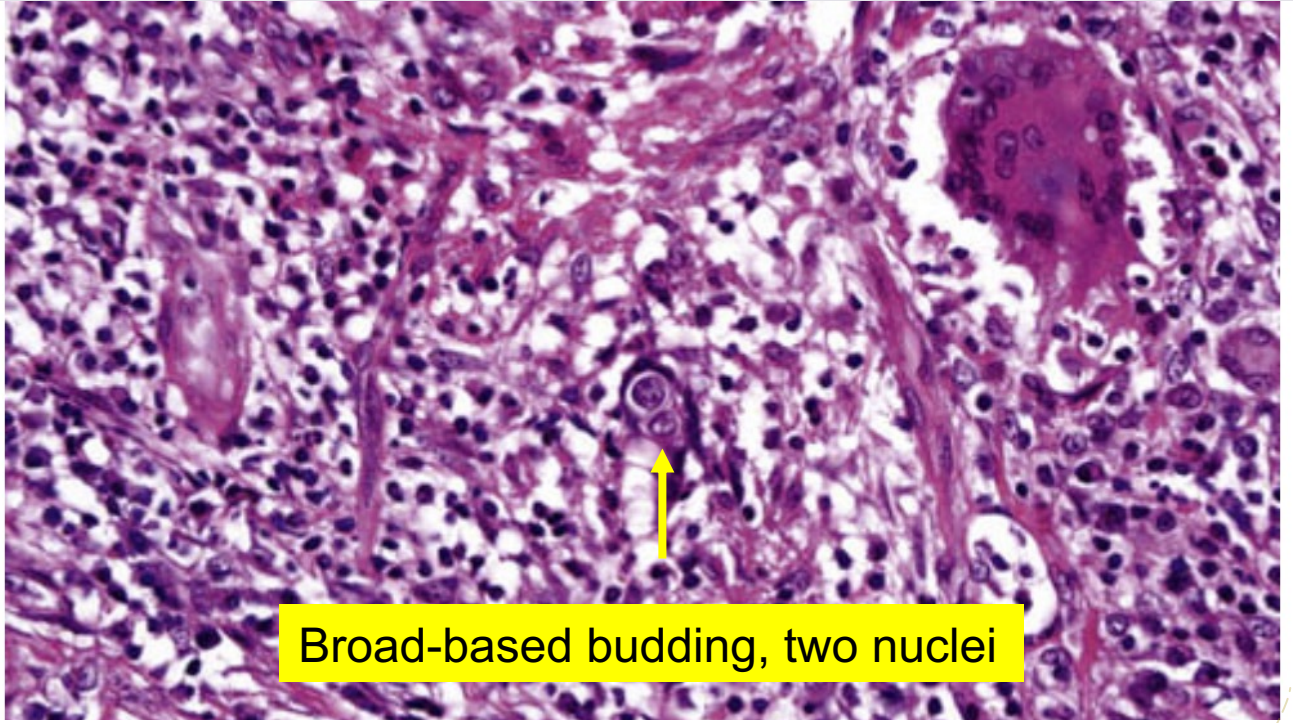
- Caused by *Cryptococcus neoformans*
- Found in soil contaminated with bird and bat excreta
- Usually inhaled, can disseminate to brain, meninges, and cerebral fluid
- Skin lesions: papules, pustules, nodules, and cellulitis.
- Most common systemic, fungal infection in AIDS patients
- Large aggregate 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
- Acid blue and mucicarmine stain capsule
- Differential diagnosis: blastomycosis, histoplasmosis, global mycosis

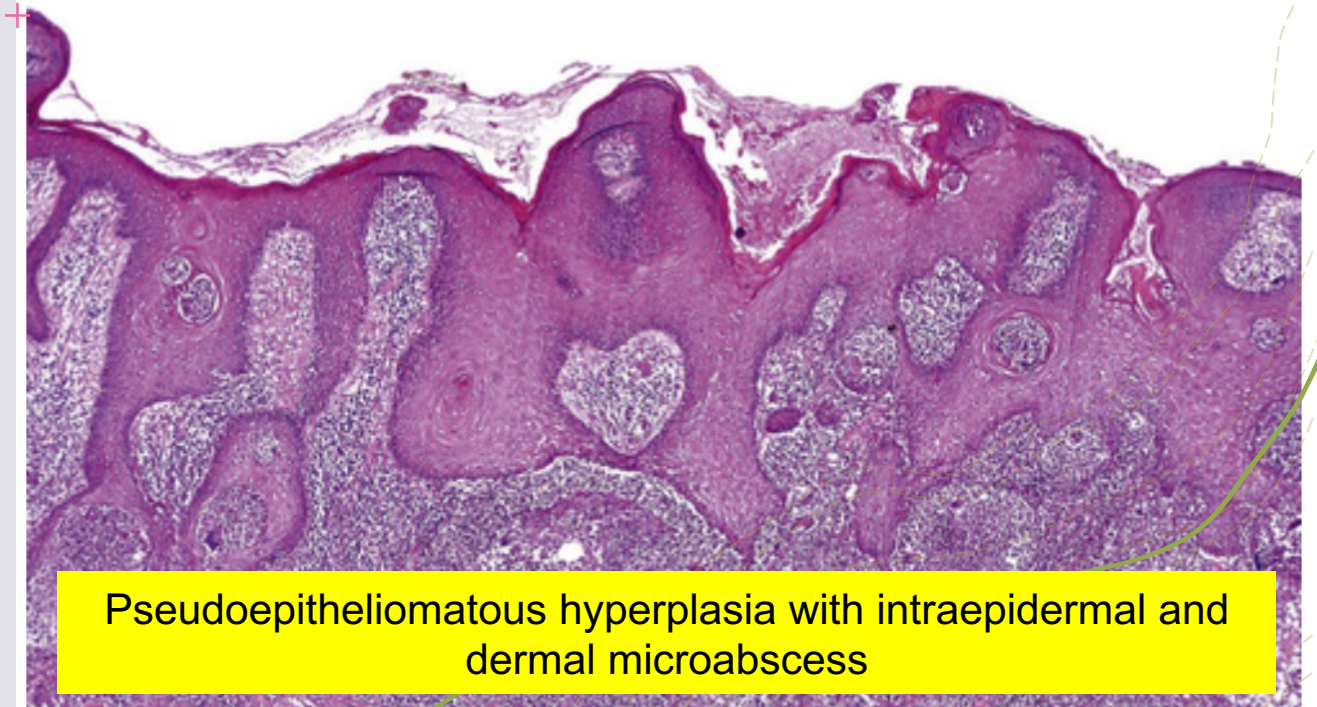




North American blastomycosis

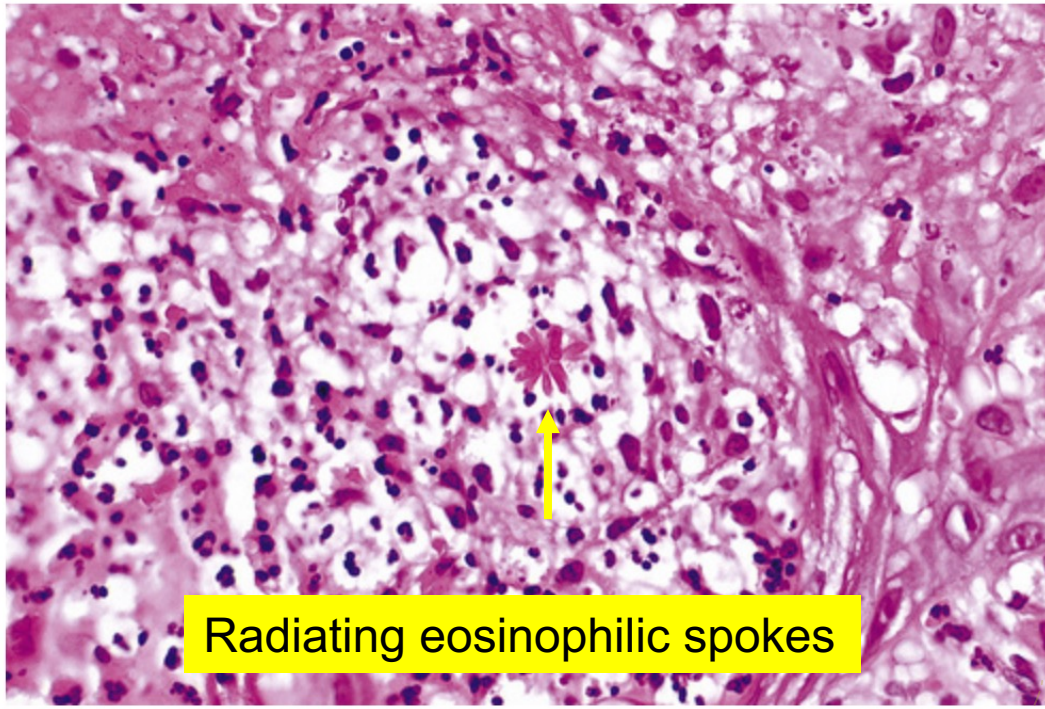
- *Blastomyces dermatitidis*
- Dimorphic fungus, acid soil in wooded areas
- Endemic in South Central and Southeastern US
- Outdoor exposure, men 20-50 to years of age
- Cutaneous involvement in 70% of patients with disseminated disease
- Verrucous plaques with peripheral pustules: face and mucosa
- 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

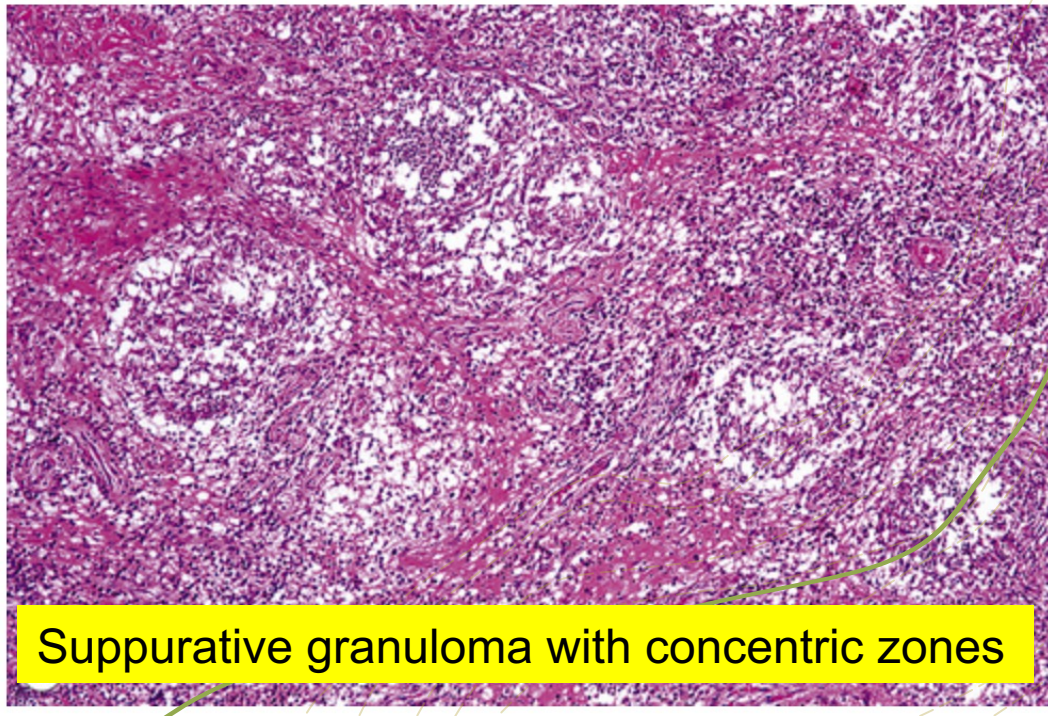




Dematiaceous fungi: Sporotrichosis

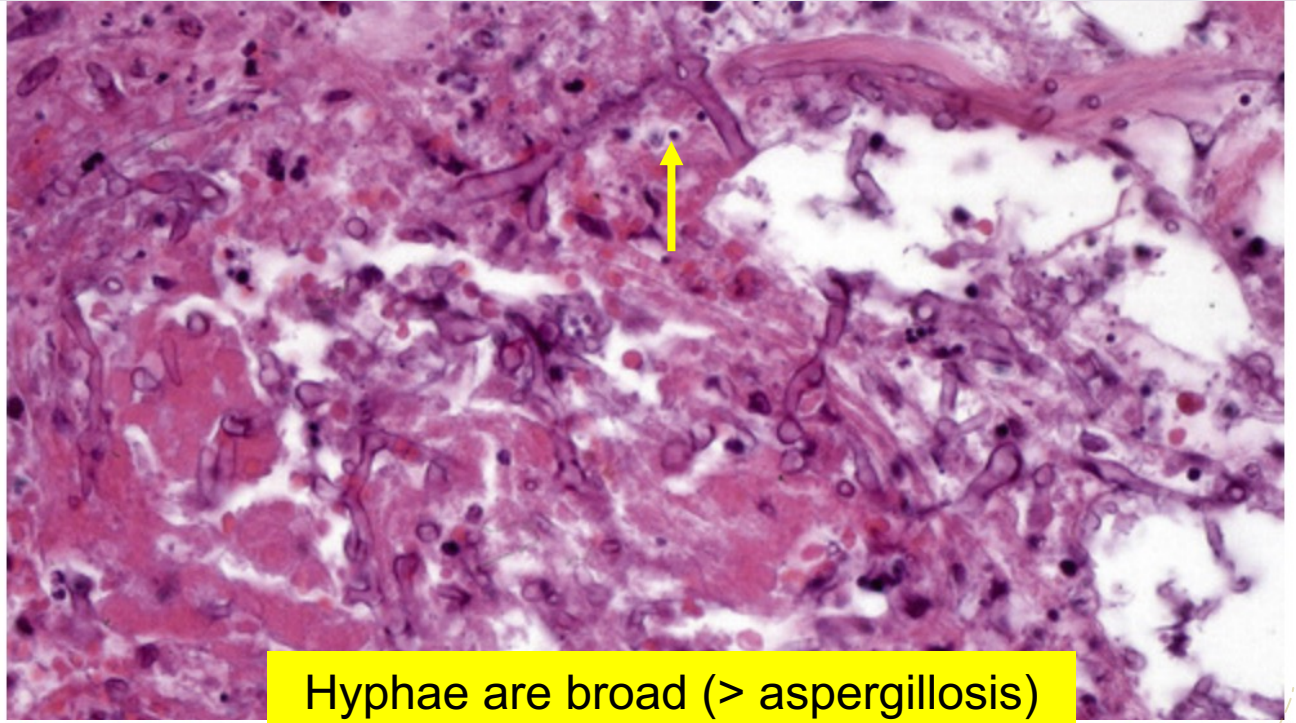
- *Sporothrix Schenckii*
- Trauma inoculates into skin --> cutaneous/subcutaneous nodules, involvement of lymphatics
- Three forms: lymphocutaneous, fixed cutaneous, and disseminated
- Early: non-specific infiltrate of lymphocytes, neutrophils, and plasma cells
- Established:
  - Pseudoepitheliomatous 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)



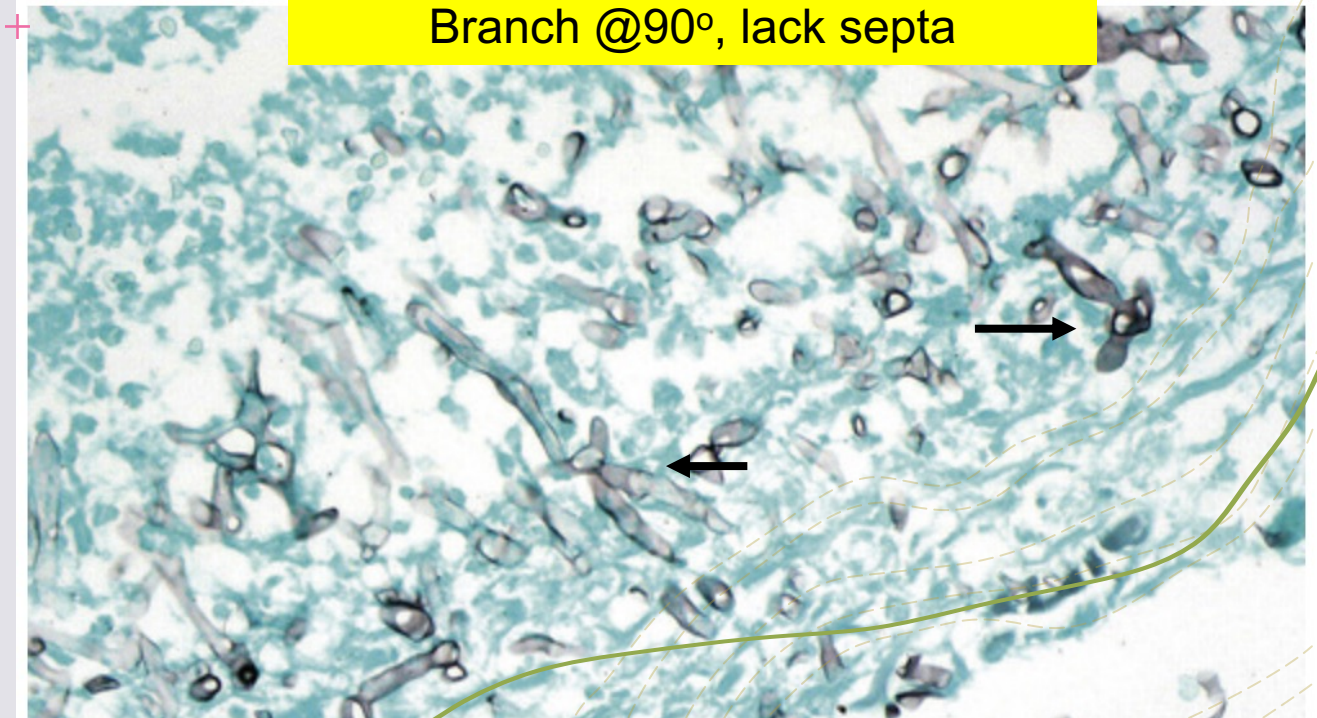


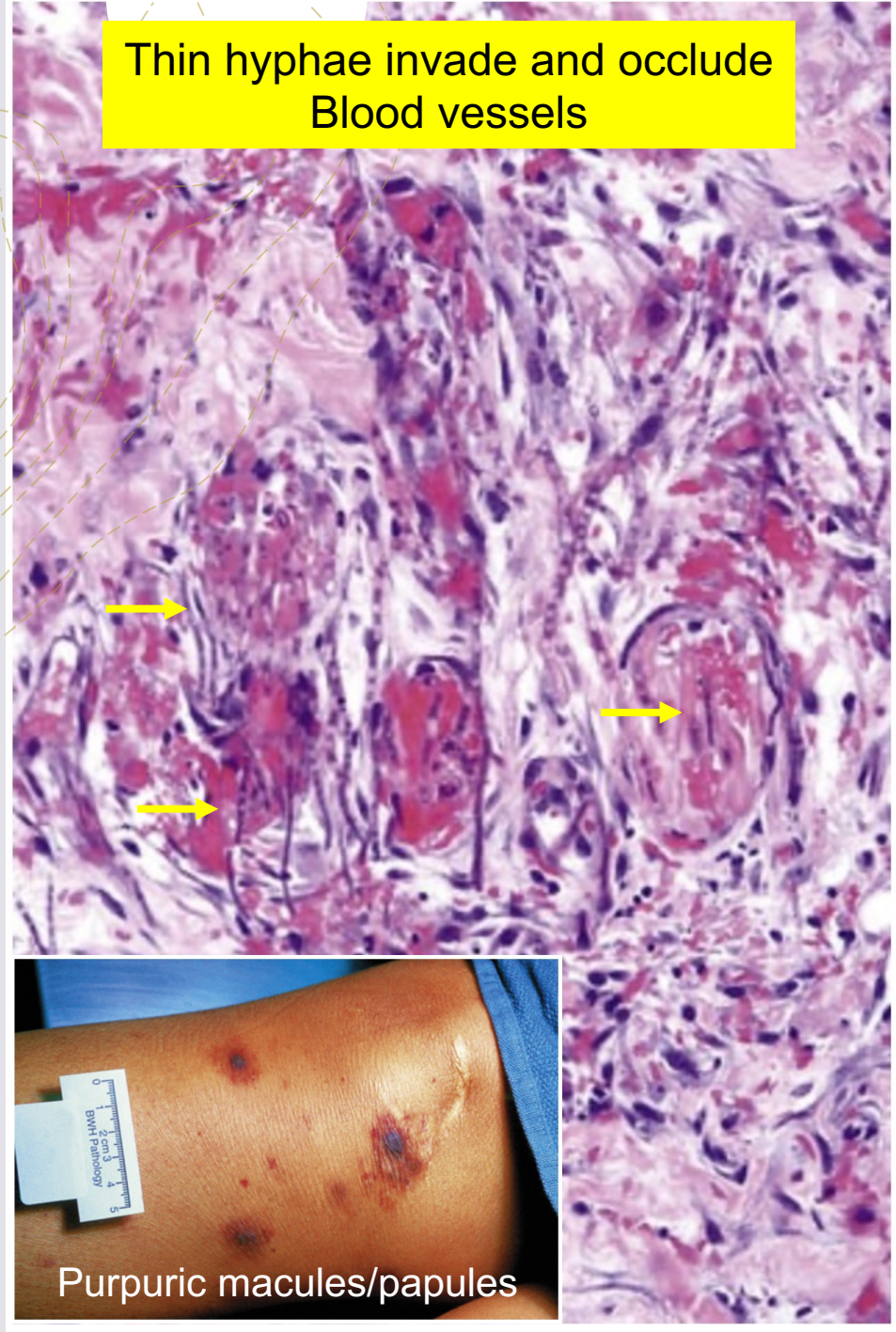
Mucormycosis

- *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



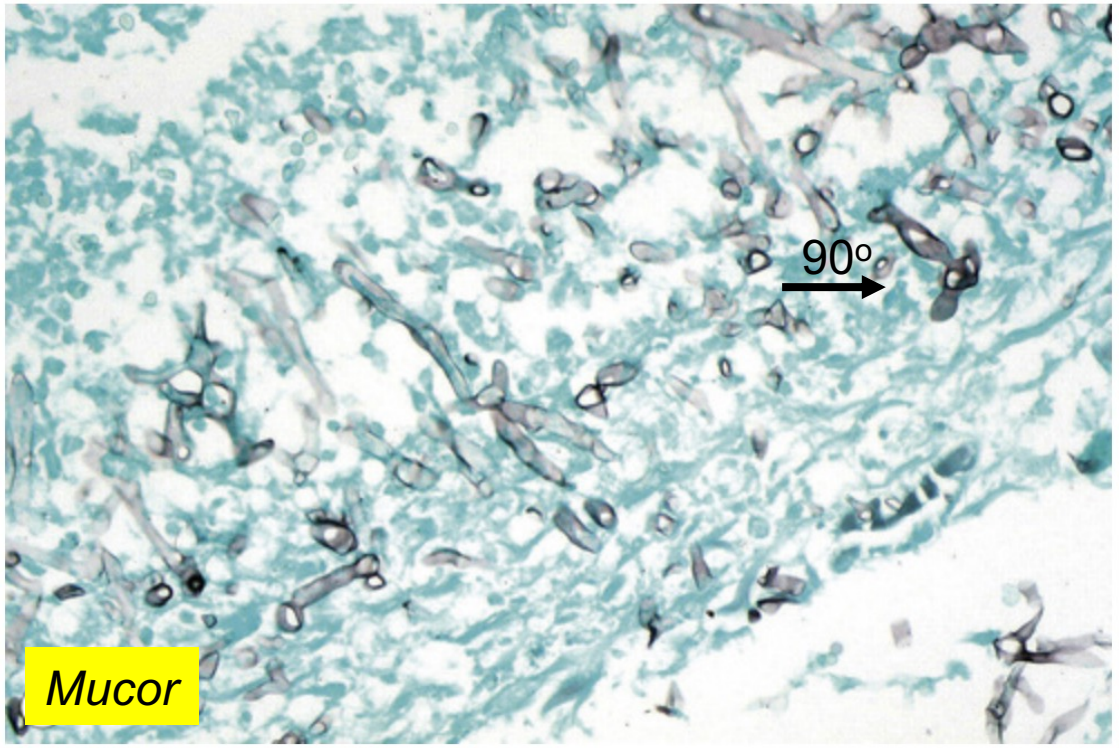


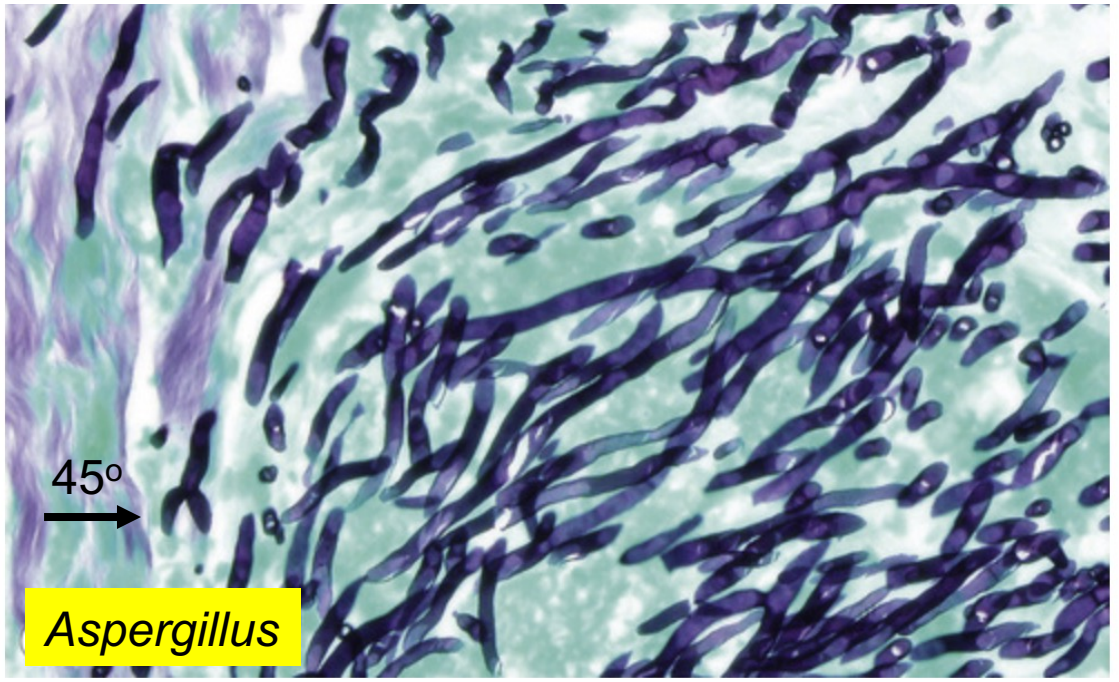
Aspergillosis

- *Aspergillus flavus, A. niger* and *A. fumigatous*
- 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

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



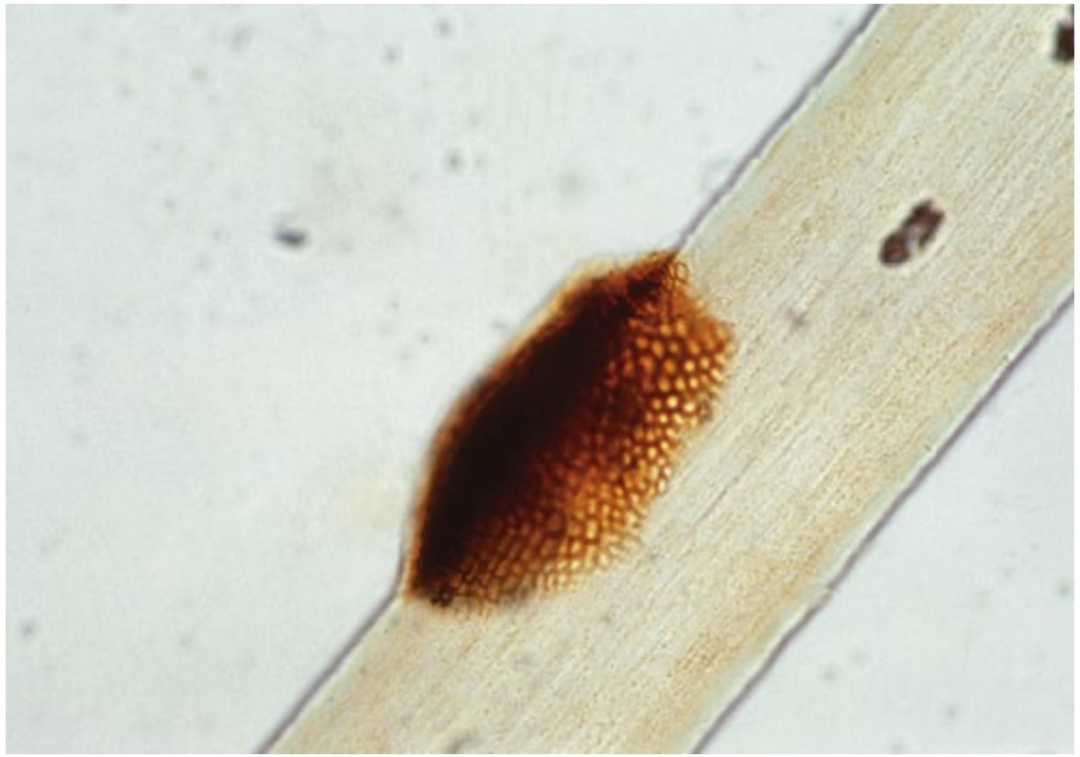


What is the expected histopathologic reaction pattern in Piedra infection?

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

Piedra (stone) and Trichospornosis

	Black Piedra	White Piedra
Causing species	*Piedra hortae*	*Trichosporon*
Environment	Tropics	Semitropical, temperate
Anatomic areas	Scalp	Beard, axillary, or groin hairs
Color	Hard, dark	Soft, light
Adherent nodules	Tight	Easily scarped off
Skin & hair follicles	Normal	Normal
Hair breakage	No	Yes
	Dark hyphae & spores	Blastoconida, arthroconida
DDX	Pediculosis, trichomycosis, trichorrehxis, 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 infection?

A. Dermal neutrophilic pustules

B. Granulomatous inflammation

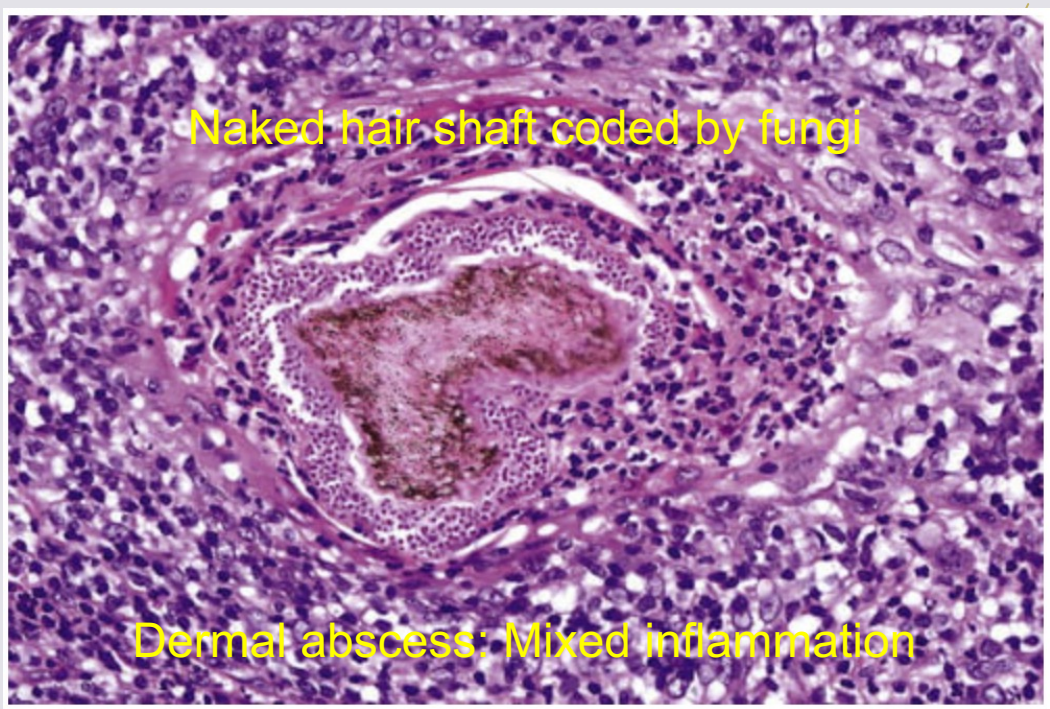
C. Normal

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*?

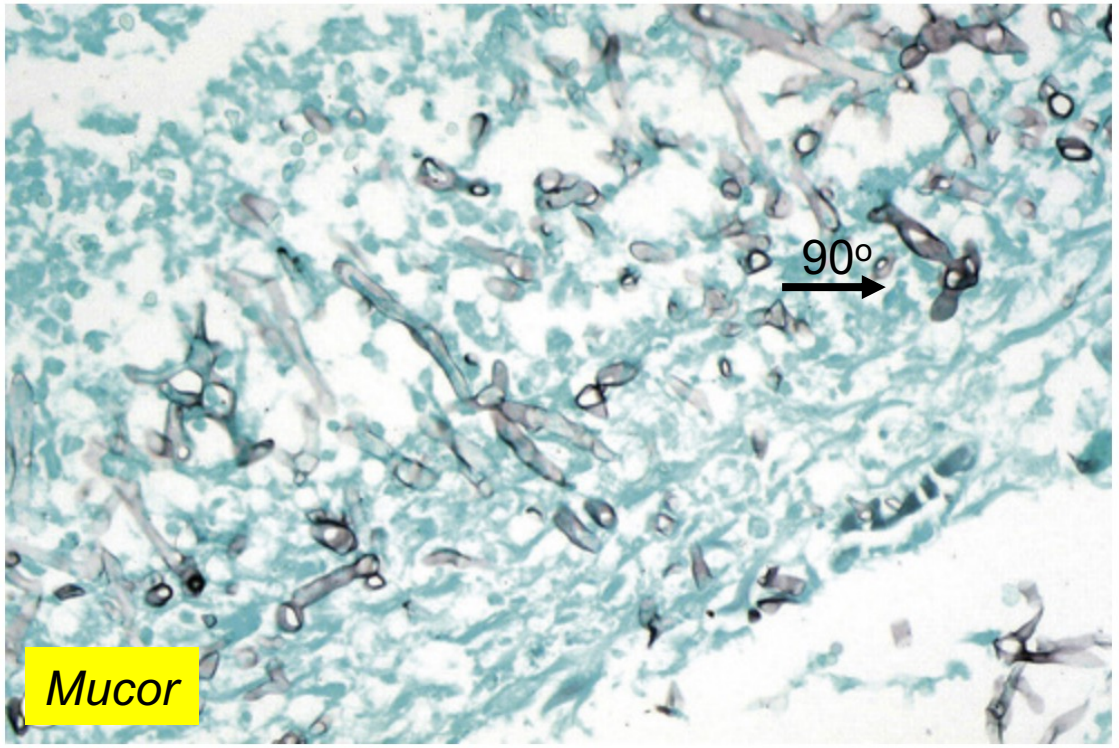
2. Which fungal species displays septa? *Aspergillus* or *Mucor*?

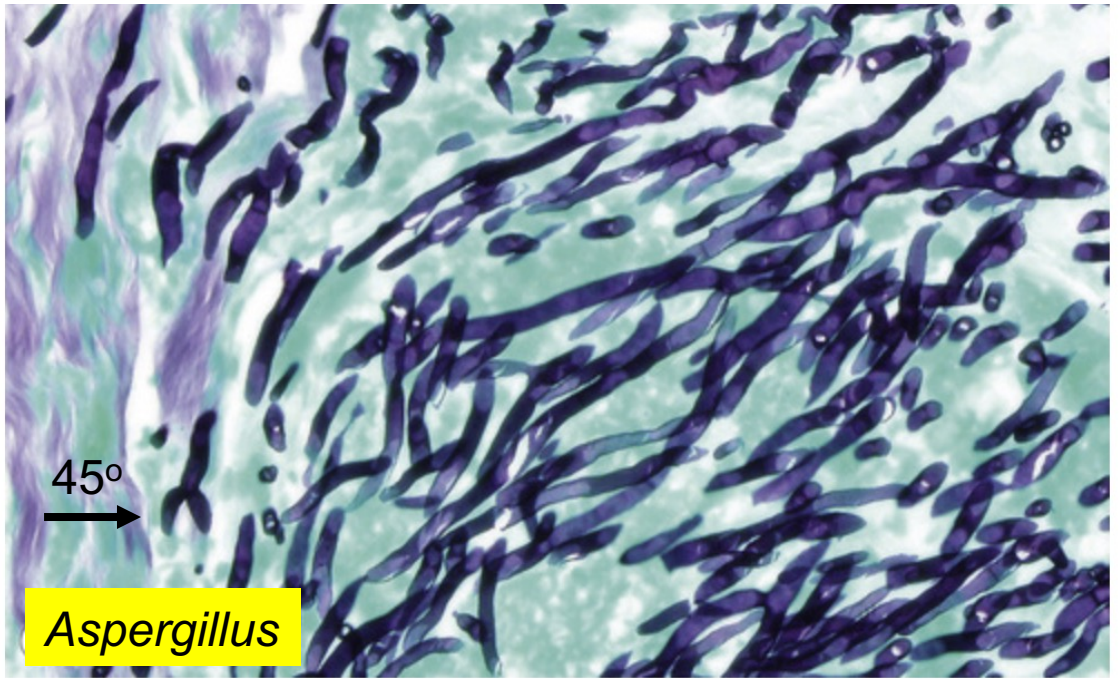
3. Which fungal species displays 90º hyphae branch ? *Aspergillus* or *Mucor*?

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

Aspergillus vs. *Mucor*: both angioinvasive

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

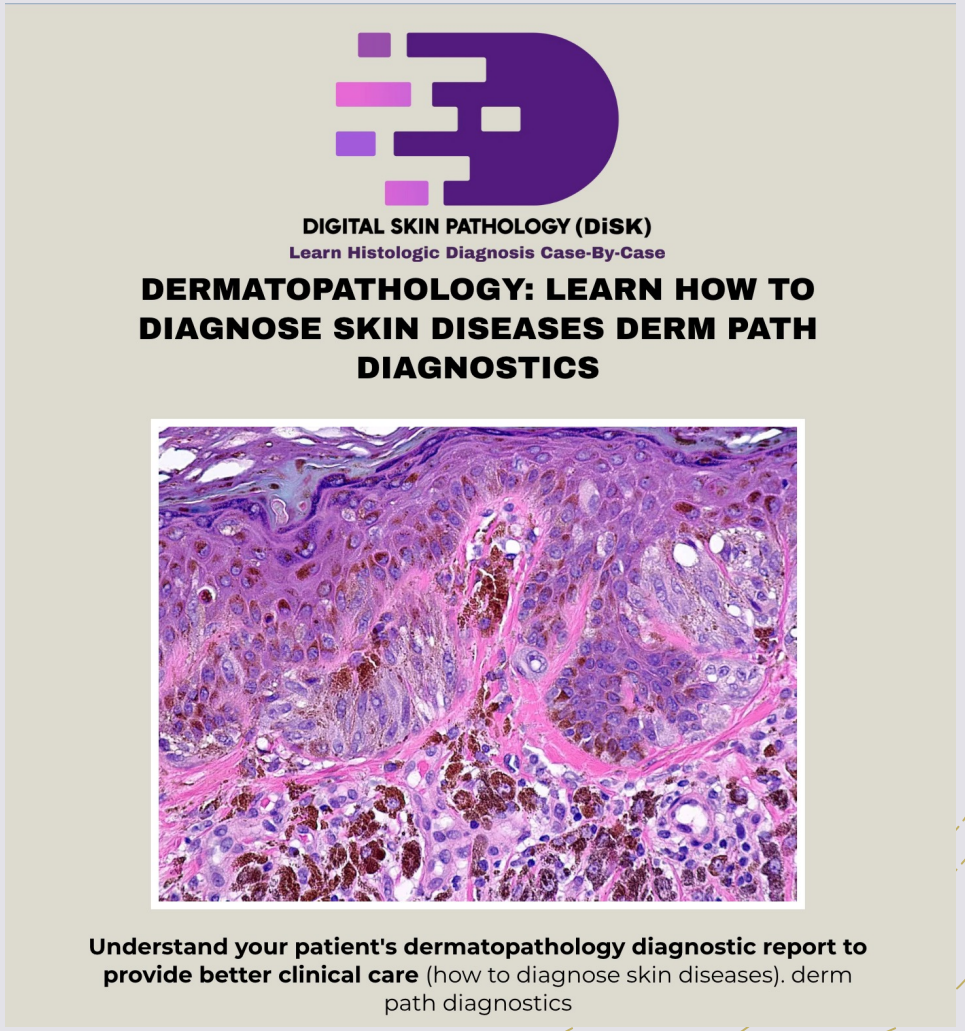




Digital Skin Pathology

https://digitalskinpathology.com/

- Example of Tinea genitalis



References

+ Weedon’s skin pathology
+ McKee’s pathology of the skin