

Painless skin nodules in a patient with a [REDACTED] transplant

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Middle-aged [REDACTED] with a history of [REDACTED] s/p [REDACTED]
[REDACTED] transplant presenting with painless lower
extremity skin nodules

Middle-aged [REDACTED] s/p [REDACTED] transplant with lower extremity skin nodules

- First noticed painless nodule few months prior to presentation
- Lesion increased in size over time but remained non-tender; subsequently developed a similar adjacent lesion
- No fevers/chills, sweats, respiratory symptoms, sinus symptoms, or GI symptoms

Middle-aged [REDACTED] s/p [REDACTED] transplant with lower extremity skin nodules

Transplant History:

- CMV D+/R-, EBV D+/R+
- No episodes of rejection

Social/Exposure Hx:

- [REDACTED]
- No significant contact with animals
- No recent travel

Immunosuppression:

- ATG induction
- Tacrolimus
- MMF 500mg BID
- Prednisone 10mg

Antimicrobial Prophylaxis:

- Dapsone

Middle-aged [REDACTED] s/p [REDACTED] transplant with lower extremity skin nodules

Vitals:

Afebrile, HR 90s, BP 119/75, SpO2 97% on RA

Physical Exam:

HEENT: No sinus tenderness, cranial nerves intact

Lungs: CTAB

CV: RRR, no murmurs

GI: Abdomen soft, non-tender, no hepatosplenomegaly

Skin: Two non-tender nodules on leg (up to ~2cm in diameter) with surrounding skin flaking; no fluctuance or purulence; onychomycosis involving finger and toenails

Middle-aged [redacted] s/p [redacted] transplant with lower extremity skin nodules

Labs:

~~10
2.0 125~~

ANC 800
ALC 400

ANC mostly ~500-1000;
brief nadir to ~300

*Neutropenia attributed to meds

134	102	24	160
3.9	26	1.4	

LFTs: normal

POLL QUESTION 1: What do you think is the most likely cause of the skin nodules?

- Bacterial infection
- Fungal infection
- Non-tuberculous mycobacterial infection
- Parasitic infection
- Cutaneous malignancy
- Erythema nodosum and/or autoimmune condition
- Other

POLL QUESTION 2: If we establish that this is a fungal infection, what is the most likely causative organism?

- Coccidioides
- Histoplasma
- Blastomyces
- Cryptococcus
- Trichophyton
- Microsporum
- Scedosporium
- Aspergillus

Middle-aged [REDACTED] s/p [REDACTED] transplant with lower extremity skin nodules

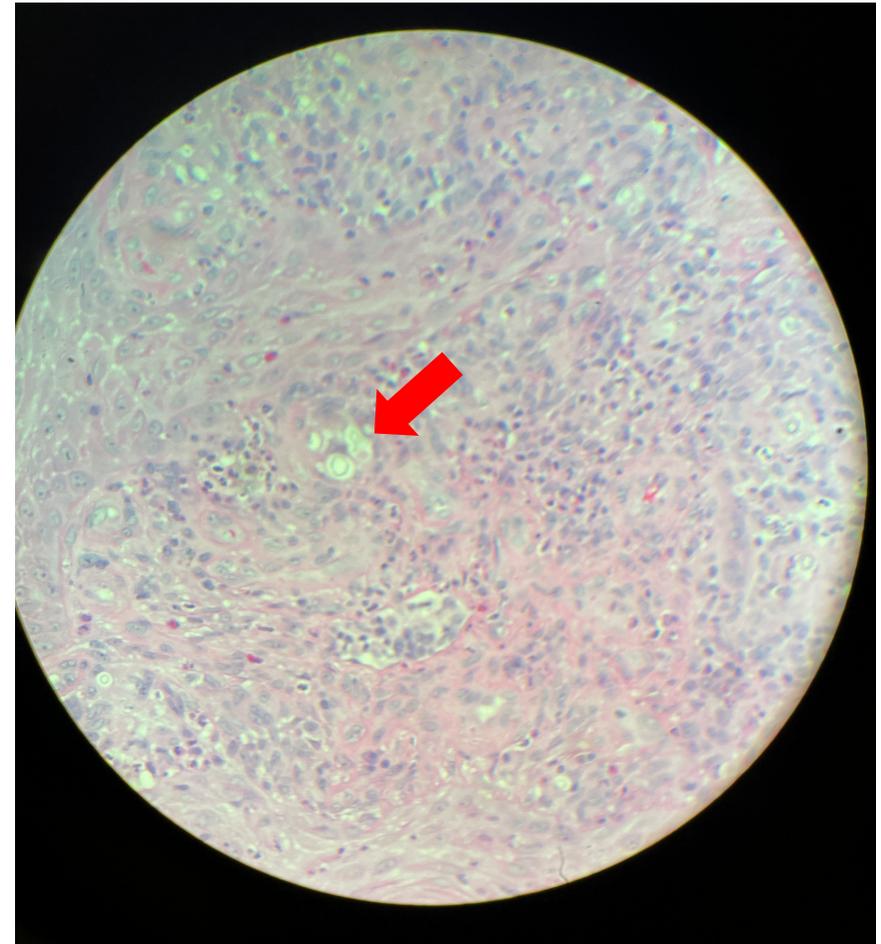
Pathology:

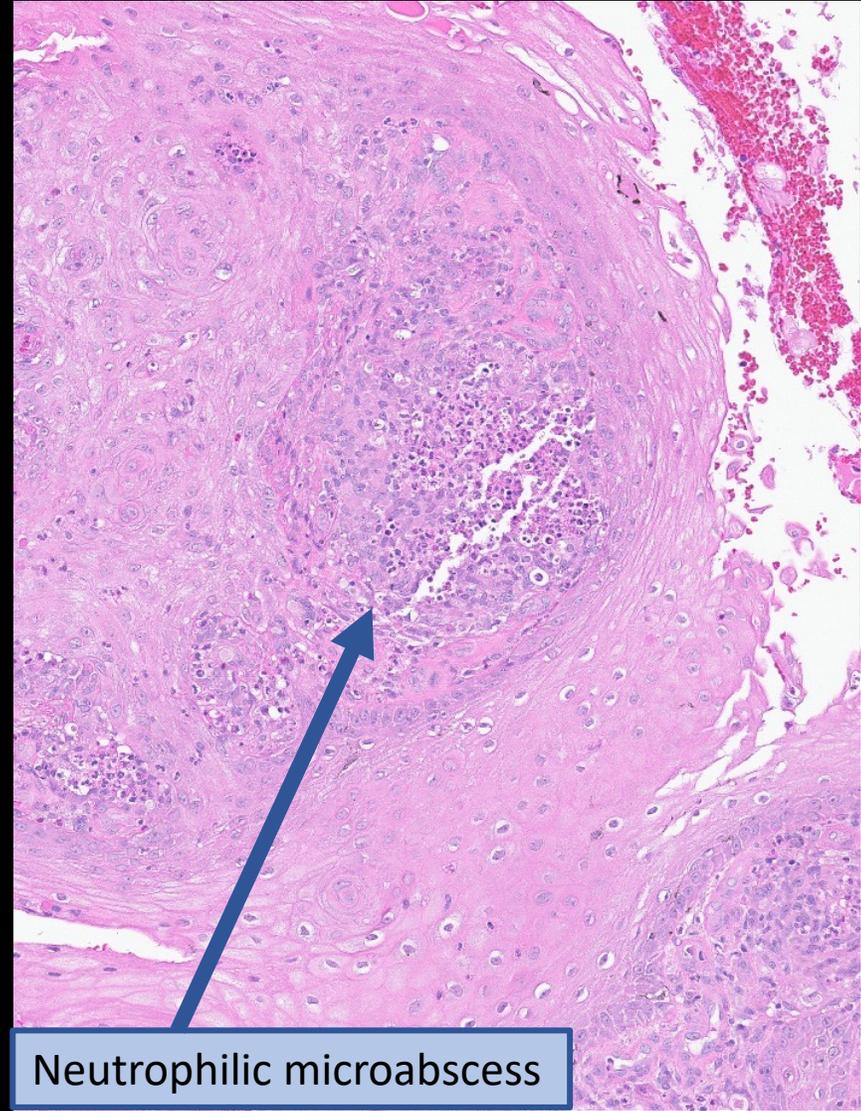
Pseudo-epitheliomatous hyperplasia with neutrophilic microabscesses and fungal yeast forms

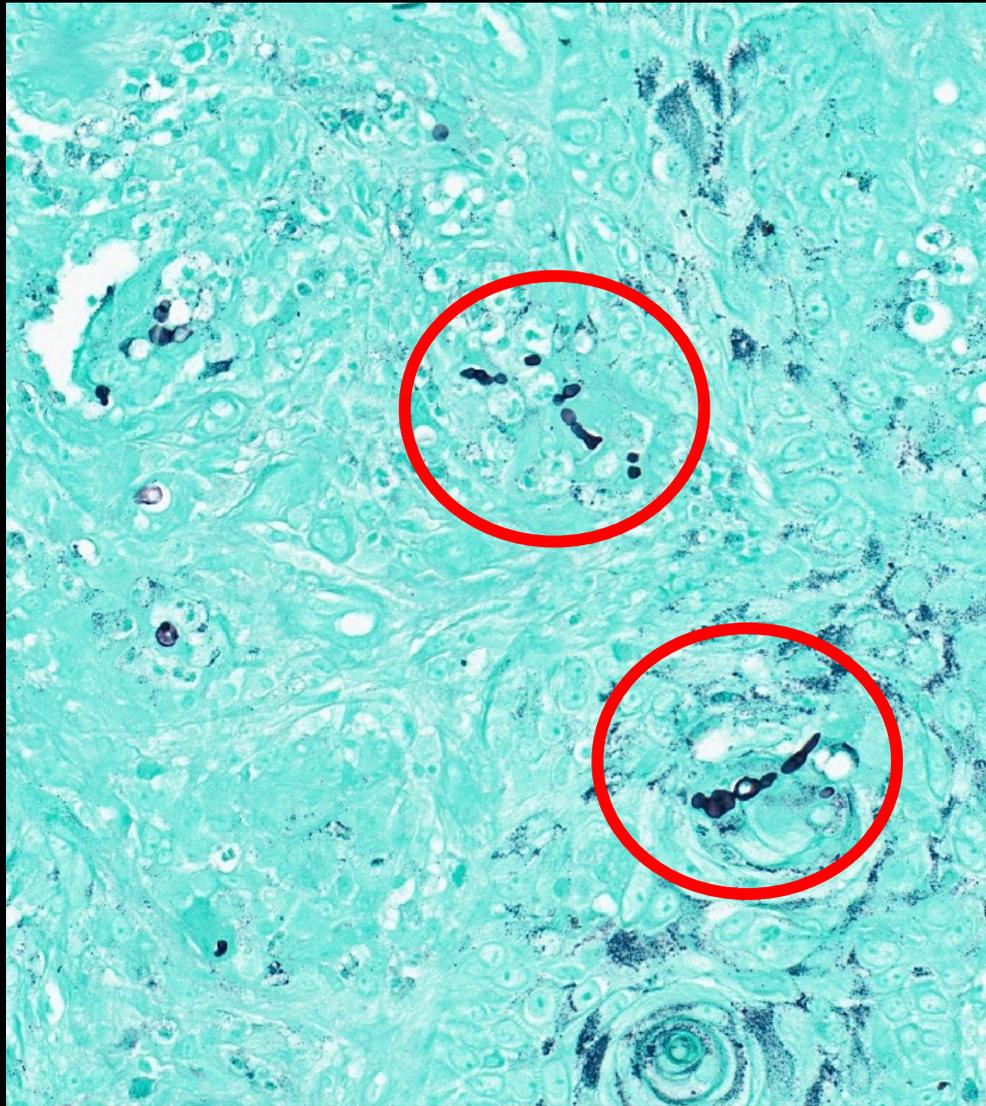
PAS and GMS stains: hyphae within hair follicle, distorted hyphae and yeast-like forms in the dermis

Microbiology:

Fungal skin culture: **Trichophyton rubrum**





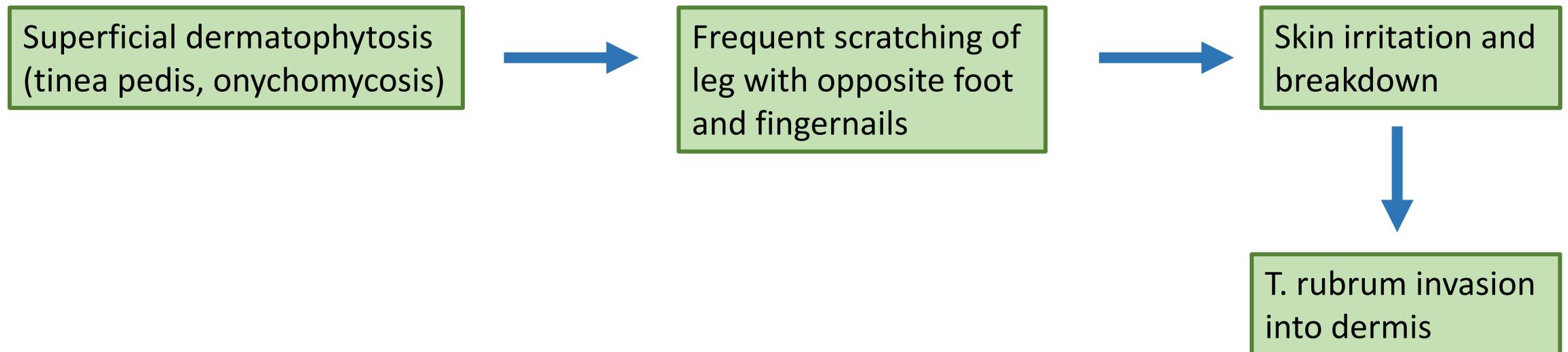


GMS stain – budding yeast-like forms and distorted hyphae

FINAL DIAGNOSIS:

Deep dermatophytosis due to *Trichophyton rubrum*

PROPOSED PATHOGENESIS:



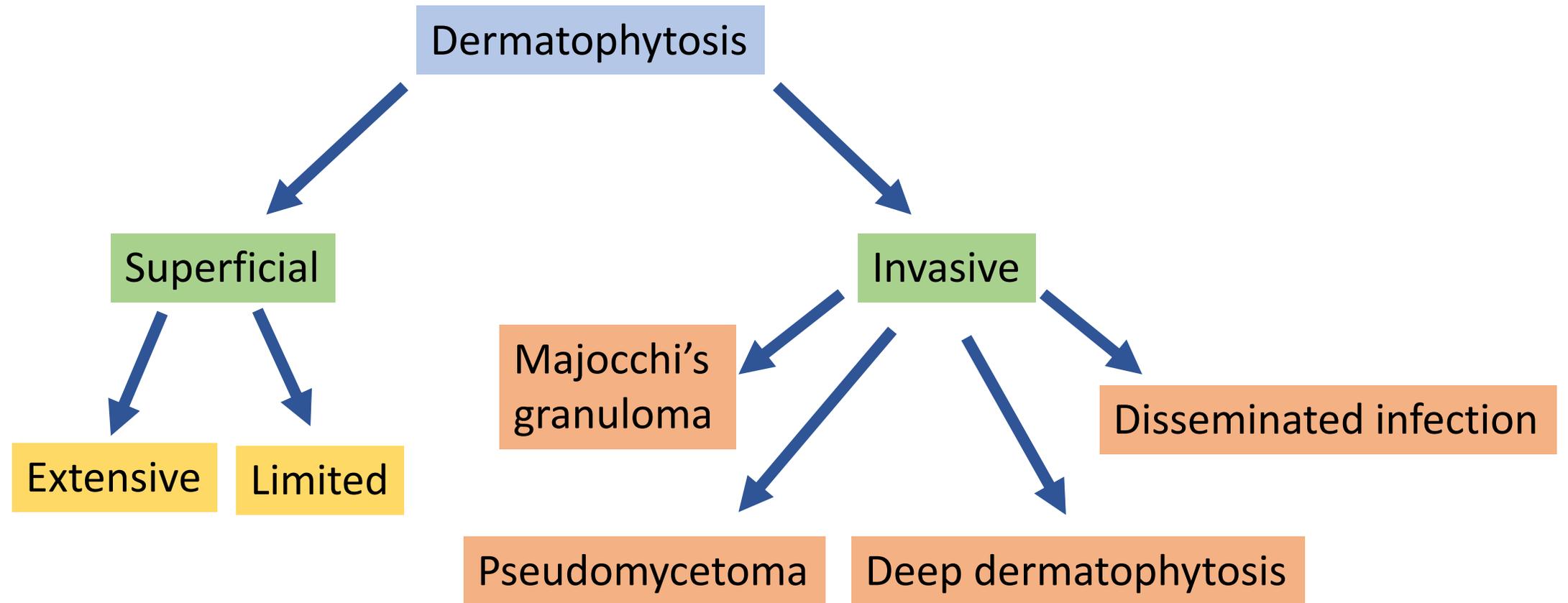
Dermatophytes

- Group of molds that is a common cause of superficial infections of keratinized tissues (ex. Tinea, onychomycosis)
- Infections due to Trichophyton species are most common; other genera include Microsporum, Epidermophyton, Nannizzia
- May cause severe and/or invasive disease in immunocompromised hosts

Severe dermatophyte infections in immunocompromised hosts

- Has been described in the setting of:
 - SOT
 - Heme malignancy
 - HIV
 - Steroids/other immunosuppressing medications
 - Liver disease/cirrhosis
 - Diabetes
 - CARD9 deficiency
- CARD9 is an intracellular signaling molecule downstream of the dectin-1 receptor which is important for the innate immune response to fungi

Classification of dermatophyte infections



Patterns of invasive dermatophytosis

MOST COMMON:

Majocchi's granuloma –
perifollicular granuloma

Deep dermatophytosis –
dermal invasion

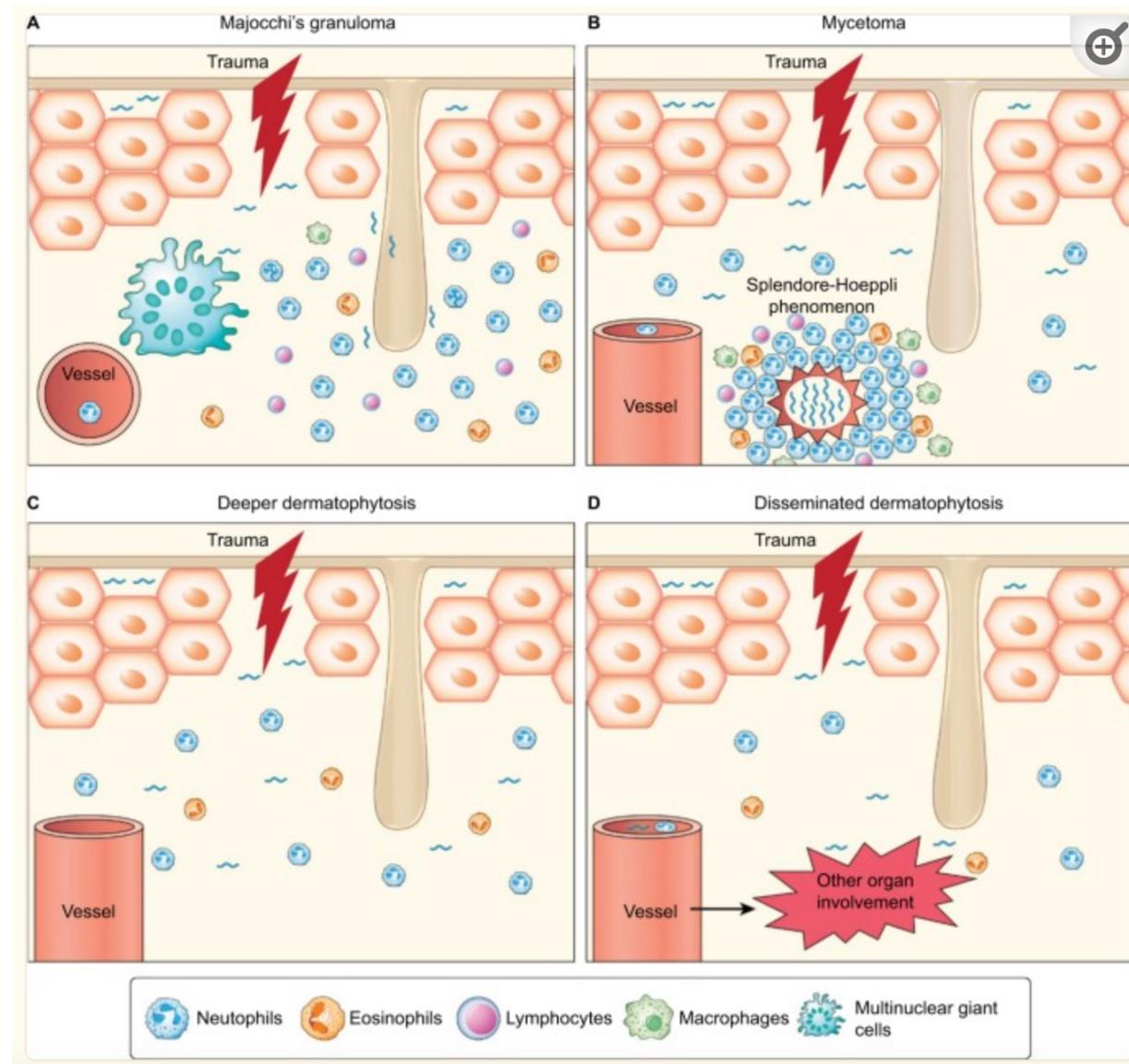


Figure extracted from: Boral H, Durdu M, Ilkit M. Majocchi's granuloma: current perspectives. Infect Drug Resist. 2018 May 22;11:751-760. CC BY-NC 3.0.

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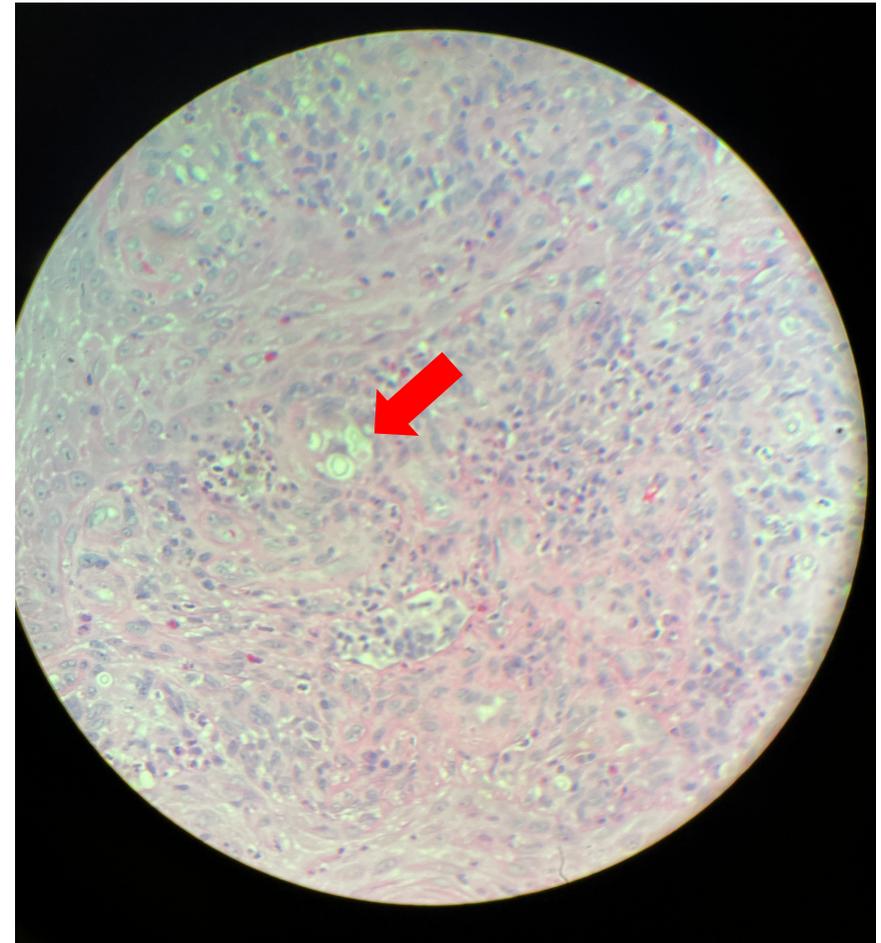
Path:

Pseudo-epitheliomatous hyperplasia with neutrophilic microabscesses and fungal yeast forms

Dermatophytes are molds not yeast....

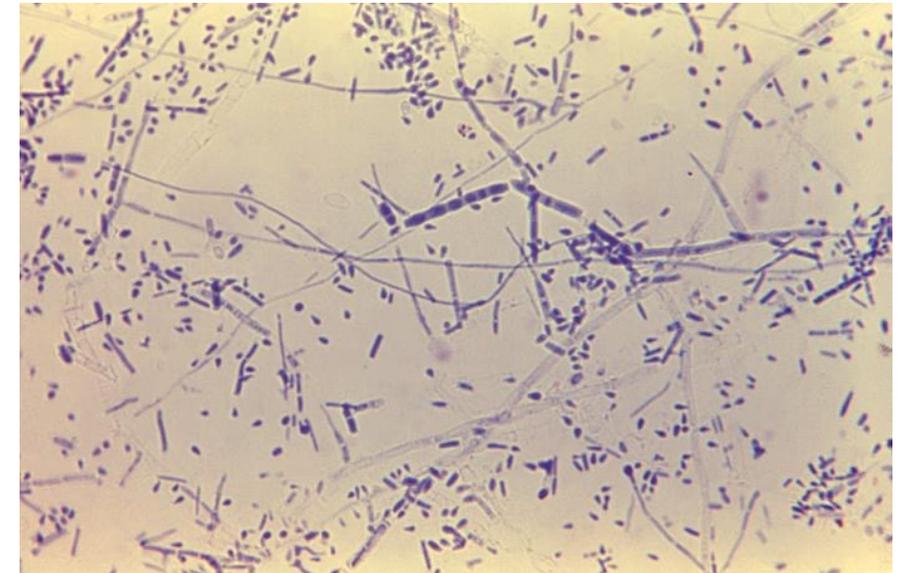
Micro:

Fungal skin culture: *Trichophyton rubrum*



T. rubrum may adopt an atypical histologic appearance in the setting of invasive disease

- Case reports of invasive T. rubrum resembling yeast (particularly Blastomycosis) on histology
- Why might this be?
 - Lillis et al hypothesize that specific conditions in the dermis may allow for T. rubrum pleomorphism
 - Hyphae and/or conidia could look like yeast if sliced at a particular angle on tissue section
- Important to obtain micro or molecular diagnosis



CDC PHIL/ Dr. Lucille K. Georg

POLL QUESTION 3: Which systemic antifungal treatment would you choose for invasive *T. rubrum* infection?

- Terbinafine
- Fluconazole
- Itraconazole
- Posaconazole
- Voriconazole
- Combination therapy (i.e. terbinafine + an azole)

Treatment of invasive dermatophytosis

- No official treatment guidelines
- Optimal treatment regimen is not known
- Experience is based on case series, case reports, systematic reviews

Severe dermatophytosis in solid organ transplant recipients: A French retrospective series and literature review

Claire Rouzaud¹ | Olivier Chosidow² | Anabelle Brocard³ | Sylvie Fraitag⁴ |
Anne Scemla⁵ | Dany Anglicheau⁶ | Jean-David Bouaziz⁷ | Nicolas Dupin⁸ |
Marie-Elisabeth Bougnoux⁹ | Roderick Hay¹⁰ | Olivier Lortholary^{1,11} |
Fanny Lanternier^{1,11}  and the French Mycoses Study Group^a

- Retrospective review of 12 cases in France (9 with invasive disease)
- Majority were kidney transplant recipients
- Most common presentation was lower extremity nodule, *T. rubrum* was most common organism
- No cases of disseminated disease

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- Most common systemic antifungals: terbinafine, posaconazole
- Median treatment duration ~7 months for invasive disease
- Of the 9 patients with invasive disease:
 - 5 with complete response
 - 1 partial response
 - 2 deaths
 - 1 recurrence

Treatment of invasive dermatophytosis

- Terbinafine is the most commonly used systemic agent; also experience with posaconazole and itraconazole in the literature
- Topical agents may be used in combination with systemic therapy
- Occasional role for surgical excision
- Reduce immunosuppression as able
- Treatment duration is on the order of months but varies based on response
- Role for combination systemic therapy?
 - Case report of disseminated *T. rubrum* infection treated with terbinafine + azole for 2 months then terbinafine monotherapy [Trottier, et al]

Rouzaud C, et al. Severe dermatophytosis in solid organ transplant recipients: A French retrospective series and literature review. *Transpl Infect Dis.* 2018 Feb;20(1).

Wang R, et al. Invasive dermatophyte infection: A systematic review. *Mycoses.* 2021 Apr;64(4):340-348. Epub 2020 Dec 9.

Marconi VC, et al. Disseminated dermatophytosis in a patient with hereditary hemochromatosis and hepatic cirrhosis: case report and review of the literature. *Med Mycol.* 2010 May;48(3):518-27.

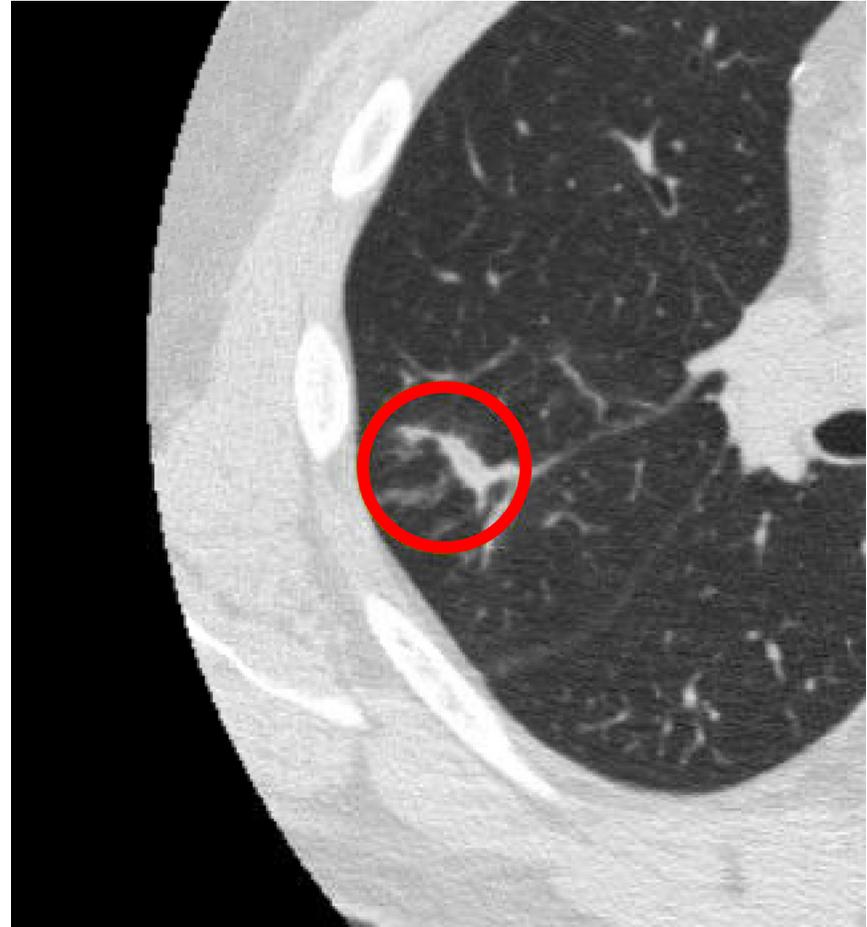
Trottier CA, et al. Beyond the Superficial: Disseminated *Trichophyton rubrum* Infection in a Kidney Transplant Recipient. *Open Forum Infect Dis.* 2020 Jul 5;7(7):ofaa281.

Back to our patient

- Started posaconazole
- Patient has no other localizing symptoms – should we pursue additional work up for disseminated infection?
 - Yes
 - No

Disseminated dermatophytosis

- Systematic review by Wang et al:
 - Disseminated infection was more common in the setting of an inherited condition (i.e. CARD9 deficiency)
 - 62.5% of disseminated cases
 - Disseminated infection associated with higher mortality
 - 37.5% compared to 6.3% for non-disseminated invasive disease
- As described in case report by Trottier et al, could consider combination therapy for severe disseminated disease



Patient outcome

- Repeat CT chest showed complete resolution of indeterminate lung density which was not felt to represent disseminated disease
- Treated with Posaconazole for 6 months with good response

Summary and take-home points

- Invasive dermatophyte infections may occur in immunocompromised hosts
- *Trichophyton rubrum* is the most commonly observed dermatophyte in both superficial and invasive disease
- *Trichophyton rubrum* is a mold but on dermatopathology it may have an atypical “yeast-like” appearance – micro/molecular diagnosis is key
- Terbinafine is the most common first-line treatment for invasive dermatophytosis described in the literature – other options include posaconazole or itraconazole
- Treatment of superficial infection could be important to prevent progression to invasive disease