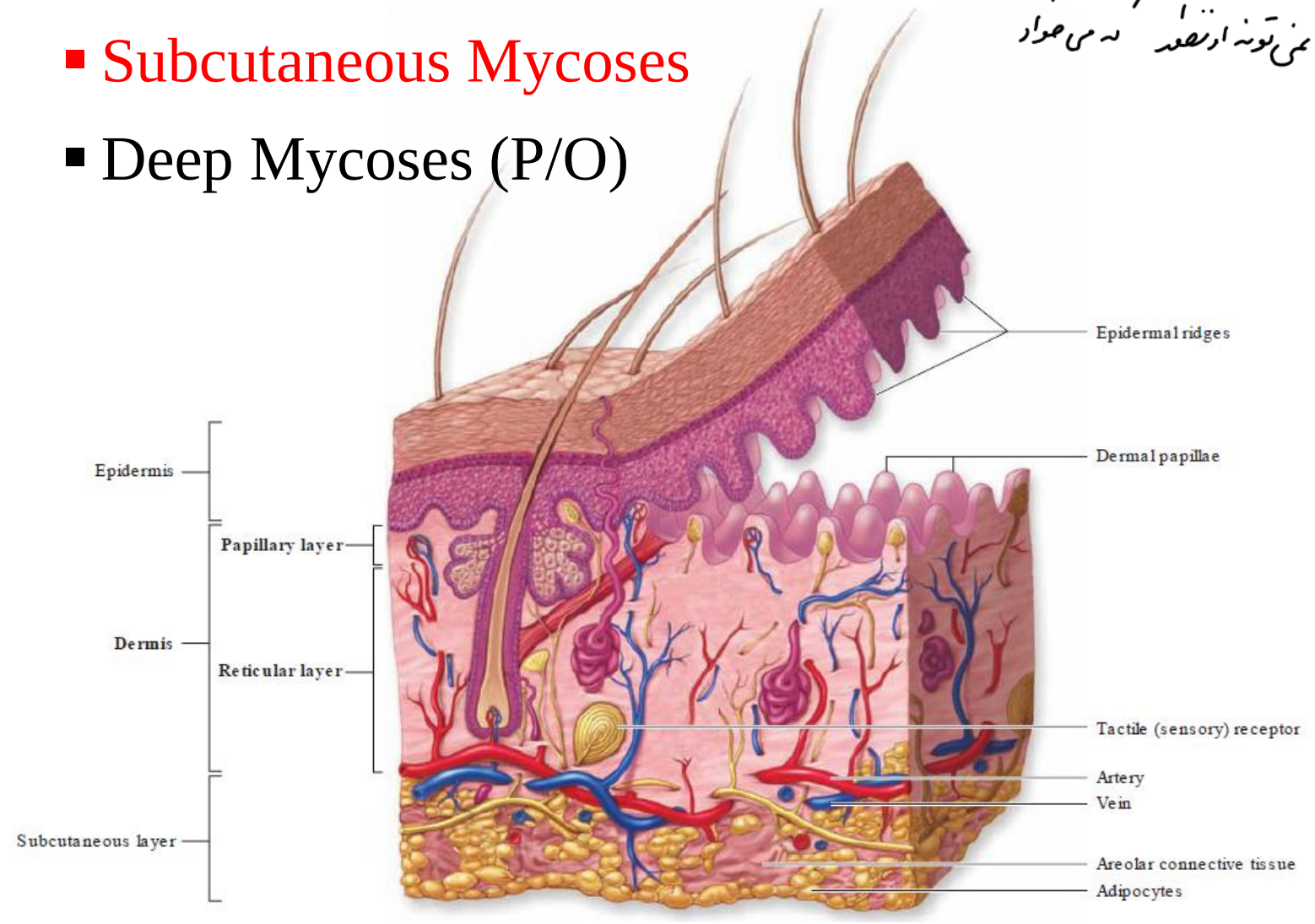
Subcutaneous Mycoses

Ali Ahmadi, Ph.D.

Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction

- Superficial Mycoses
- Cutaneous Mycoses
- Subcutaneous Mycoses
- Deep Mycoses (P/O)



- ❑ Mycetoma
- ❑ Sporotrichosis
- ❑ Chromoblastomycosis

Subcutaneous fungal infections

- Subcutaneous fungal infections are chronic conditions resulting from the traumatic implantation of a fungal organism through a superficial wound or an injury caused by thorns or plant debris.
- These infections are commonly found in tropical and subtropical regions, where they occur either endemically or sporadically.
- Lesions typically remain localized at the inoculation site but may gradually extend to adjacent tissues.
- The causative fungi of these infections are generally saprophytic in nature, residing in the environment.

epidemi → pandemic

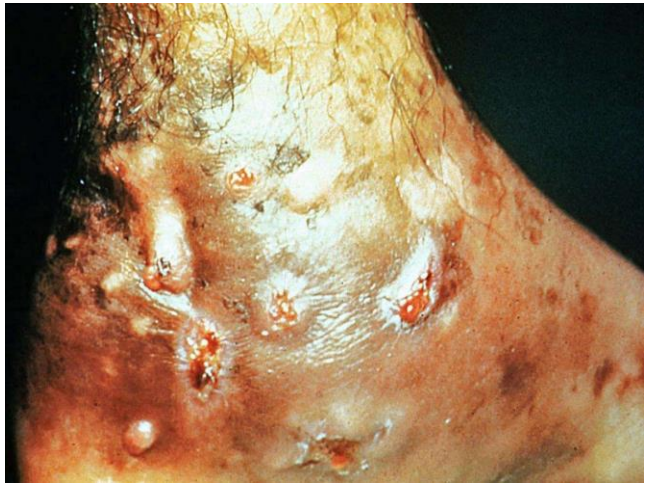
Mycetoma (Maduromycosis; Madura Foot)

- Chronic subcutaneous infection typically follows a slow and painless course, characterized by edematous lesions, purulent fistulas, and abscess formation.
- Mycetoma is a neglected tropical disease (NTD)
- Although mycetoma is primarily a subcutaneous disease, it can involve bone and lymph nodes by contiguous spread.
- It was first reported from the city of Madurai, India.
- The lesion typically appears on the foot, although all parts of the body may be affected.

Introduction

- Mycetoma shows three clinical characteristics: tumor, sinuses, and grains.
  - ✓The tumor results as a consequence of a progressive and relatively painless swelling.
  - ✓Sinuses are a characteristic of the disorder; they can be absent in early stages, but later develop and drain purulent material and grains.
  - ✓Grains are colonies of the causative agent and can be black, white, or red.

- Mycetoma showing numerous draining sinuses. There is destruction of bone, distortion of the foot, and hyperplasia at the openings of the sinus tracts.



What fungi or bacteria cause Mycetoma?

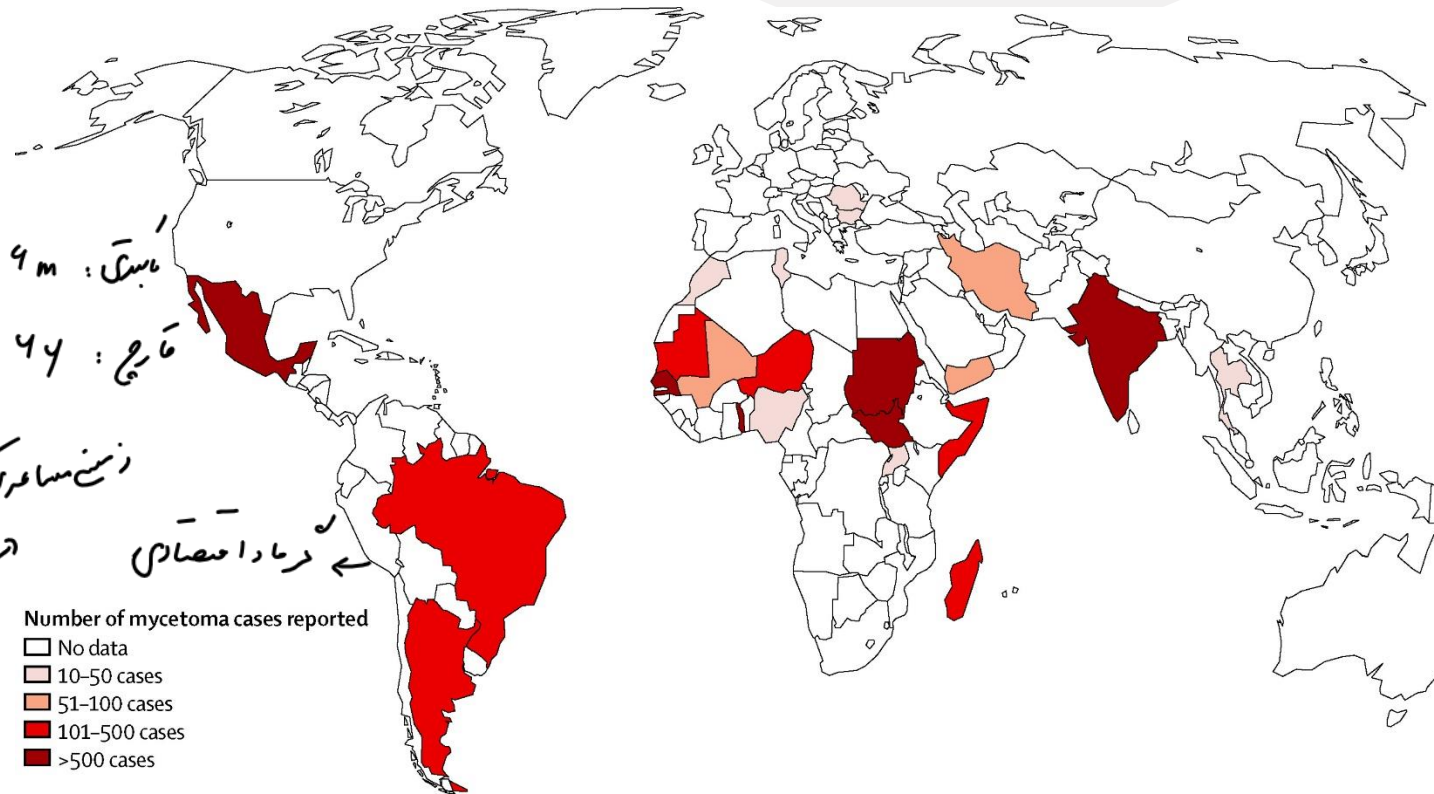
- Maduromycosis can be caused by bacteria (actinomycetoma) or fungi (eumycetoma).
- Bacteria are primarily soil-borne reservoirs, while fungi serve as exogenous sources, including soil, plants, water, and surrounding environments on objects.
- Both types of infections appear similar in clinical manifestations.
- Actinomycetoma progresses more rapidly towards bone invasion compared to eumycetoma.

Species
Actinomycetoma
Actinomadura madurae
Streptomyces somaliensis
Actinomadura pelletieri
Nocardia brasiliensis
Nocardia asteroides
Nocardia otitidiscaviarum (synonym: *Nocardia caviae*)
Actinomyces israelii
Eumycetoma
Madurella mycetomatis
Scedosporium boydii (synonyms: *Scedosporium apiospermum*, *Pseudallescheria boydii*)
Aspergillus fumigatus
Mold fungi

Epidemiology

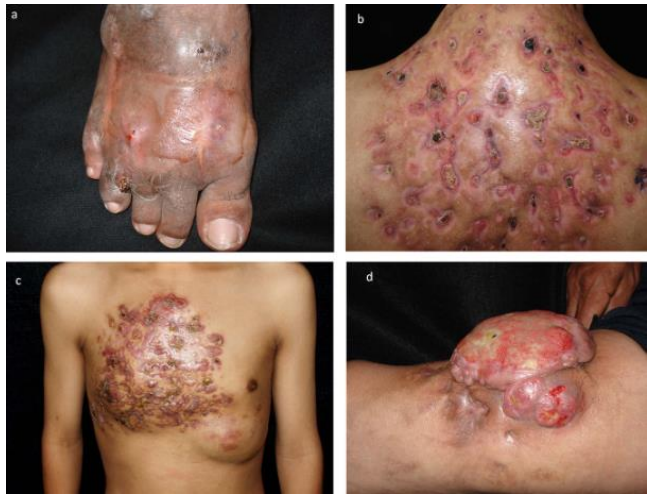
- The disease has a global distribution but predominantly occurs in tropical regions with low rainfall regions between the latitudes of 15° south and 30° north of the equator, known as the 'mycetoma belt, such as Central America (Mexico, Brazil, Venezuela), Africa (Sudan, Senegal, Somalia), and Asia (India, Iran, Bangladesh).

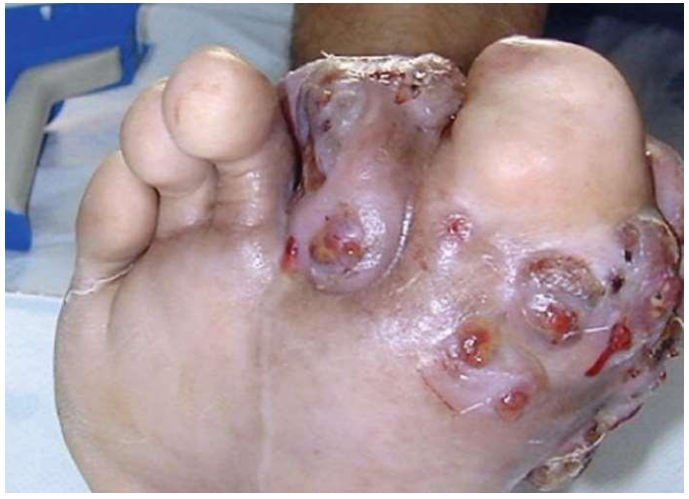
- Mean age 35 years (range: 20–50)
- Male (70%)
- Through traumatic inoculation
- Incubation period: (Long & variable)
- Farmers' most common occupation
- Although diabetes is a frequent comorbidity.

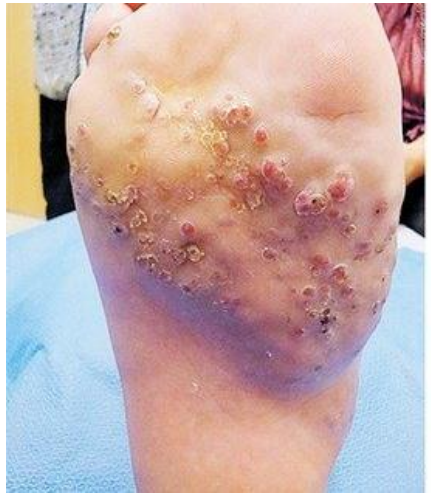


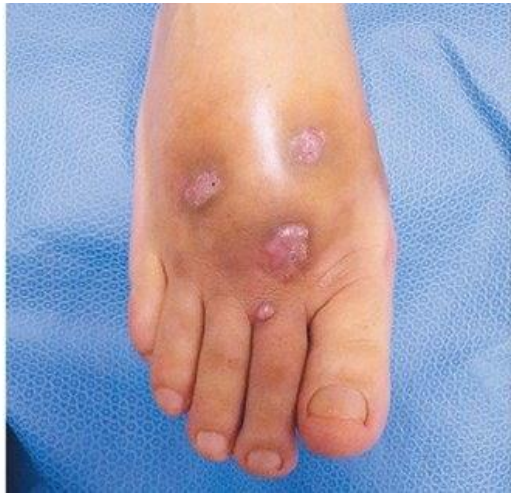
Clinical Manifestations

- lower limbs as a primary involved body region.
- Following the entry of the organism, a painless subcutaneous lesion initially presents as a papule, nodule, or abscess, which gradually softens and eventually forms fistulas that lead to the skin surface. The rupture of the abscess and the expulsion of granules from it are characteristic features of mycetoma lesions.
- The clinical course depends on the anatomic location, duration of lesions, and medical intervention.
- The most significant complication of mycetoma is deformity or disfigurement, which can lead to disability and functional impairment.



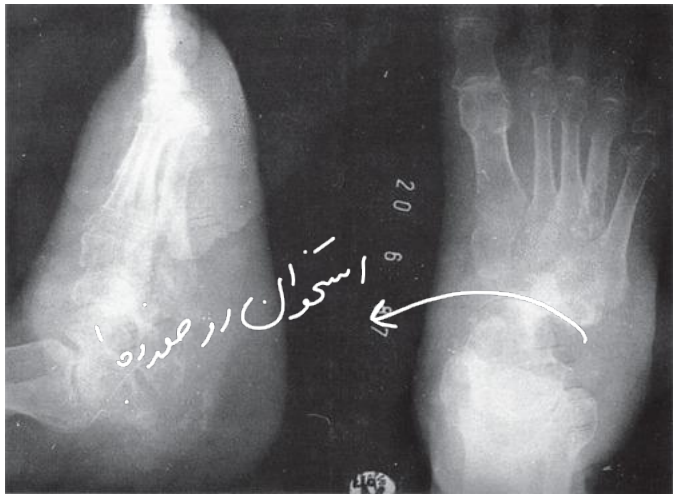


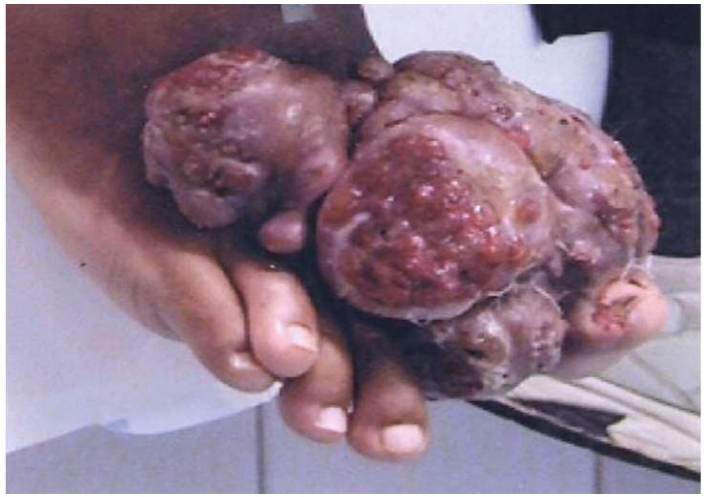




Clinical Manifestations

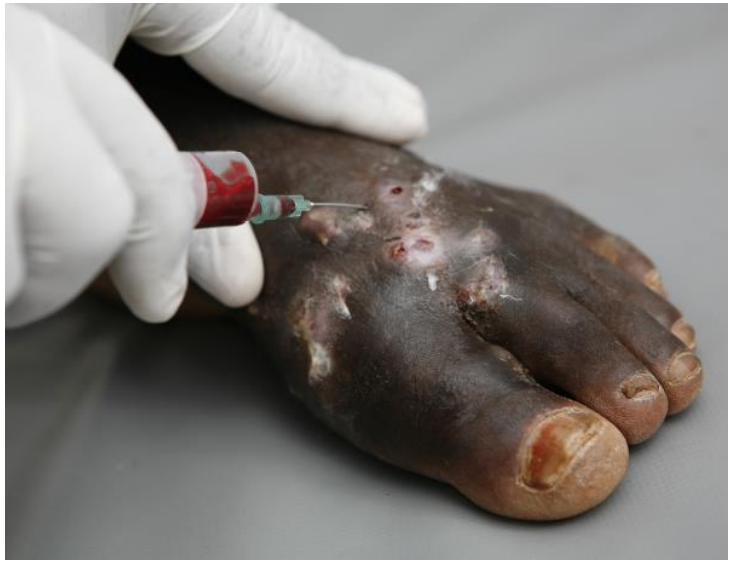
- Lymphatic spread is uncommon with eumycetomas, occurring in fewer than 3% of cases. It appears to be more frequent in actinomycetomas, possibly because the grains are smaller in this condition.
- In both eumycetoma and actinomycetoma, bone involvement occurs by contiguous spread, with changes occurring first in cortical bone. Bone involvement occurs in up to 76% of cases and is more extensive in cases with a longer disease duration.

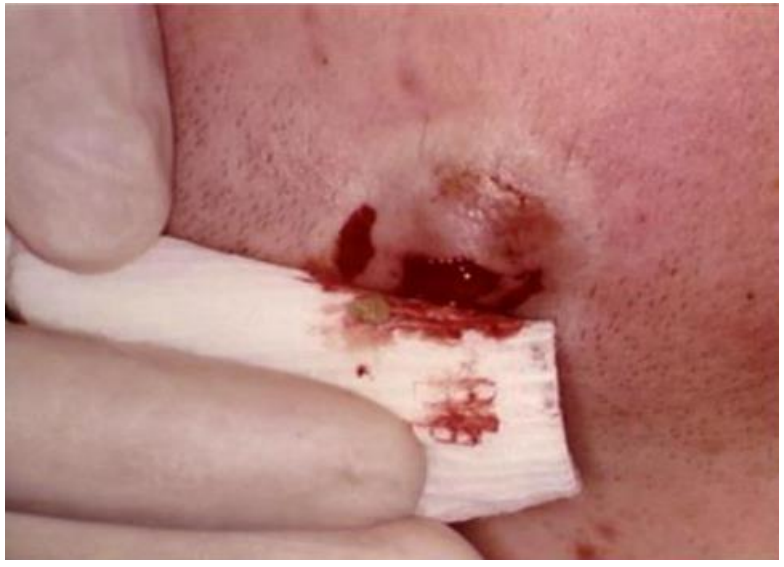




Sampling Procedure:

- Initially, the surface of the lesion or unopened fistulas is disinfected using 70% alcohol. Sterile scalpels are then used to gently open the fistulas. By applying pressure to the surrounding tissue, pus, blood, and exudates containing granules are expressed and collected into a sterile Petri dish containing sterile normal saline.
- If discharged grains are not available, a deep skin biopsy taken from a small abscess or around a sinus tract is necessary for both culture and histopathologic studies.
- Fine-needle aspiration can also be useful for the diagnosis of eumycetoma.





Diagnosis

Photography of a surgical biopsy showing a well-encapsulated eumycetoma lesion with numerous black grains.

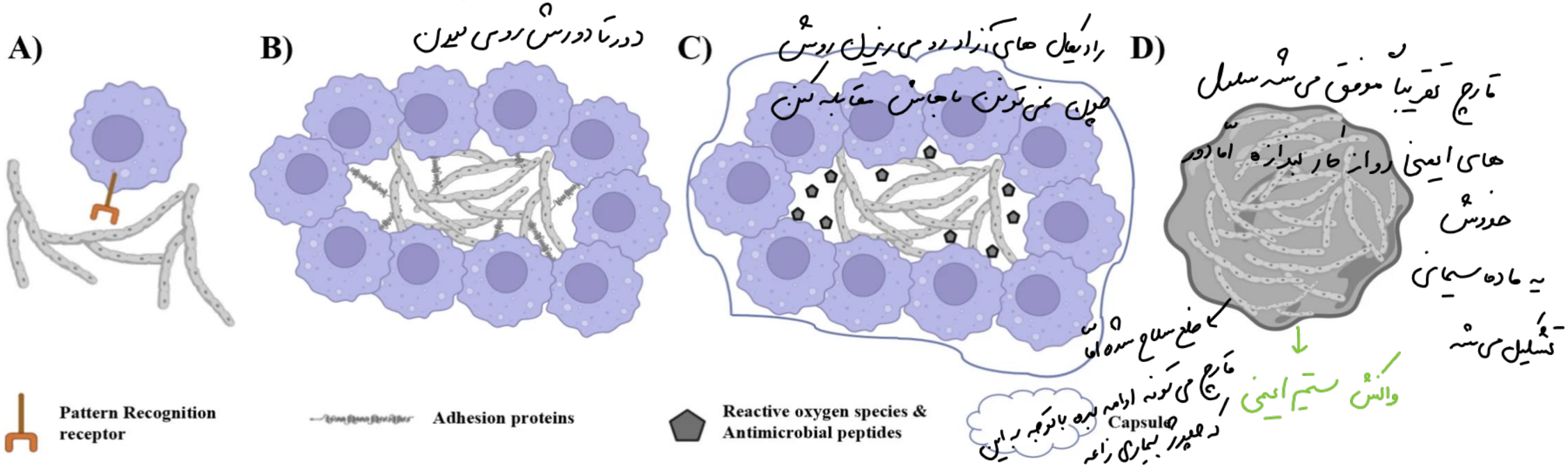
Grain formation over time.

A Fungal hyphae are recognized by Pattern Recognition Receptors as pathogens.

B Immune cells will aggregate around the hyphae, and host cell will cross-link and bind to the fungal cells.

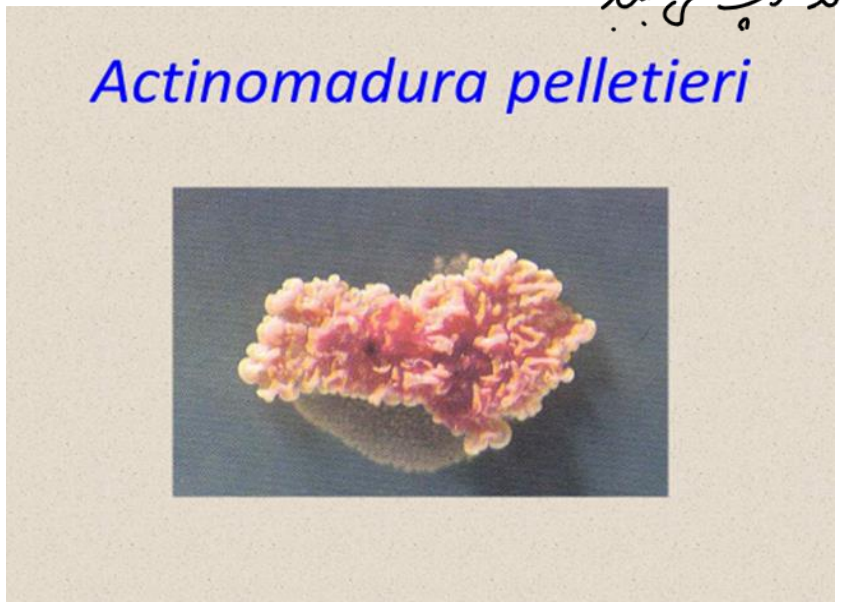
C Reactive oxygen species are produced by granulated cells. The fungus produces melanin and trehalose and forms a capsule.

D The fungus fully breaks down the host cells and creates cement material.



Evaluation of Grains:

- The granules are washed several times in sterile normal saline to remove adherent pus, blood, and fibrinous debris. These granules are visible to the naked eye and may appear in various colors, including white, brown, black, yellow, off-white, pink, and red. Their consistency ranges from soft to firm and hard.
- This direct examination will differentiate the grains of eumycetomas from the grains of actinomycetomas.



Diagnosis

حتما توی امتحان باید ذکر بشه گرانوله!

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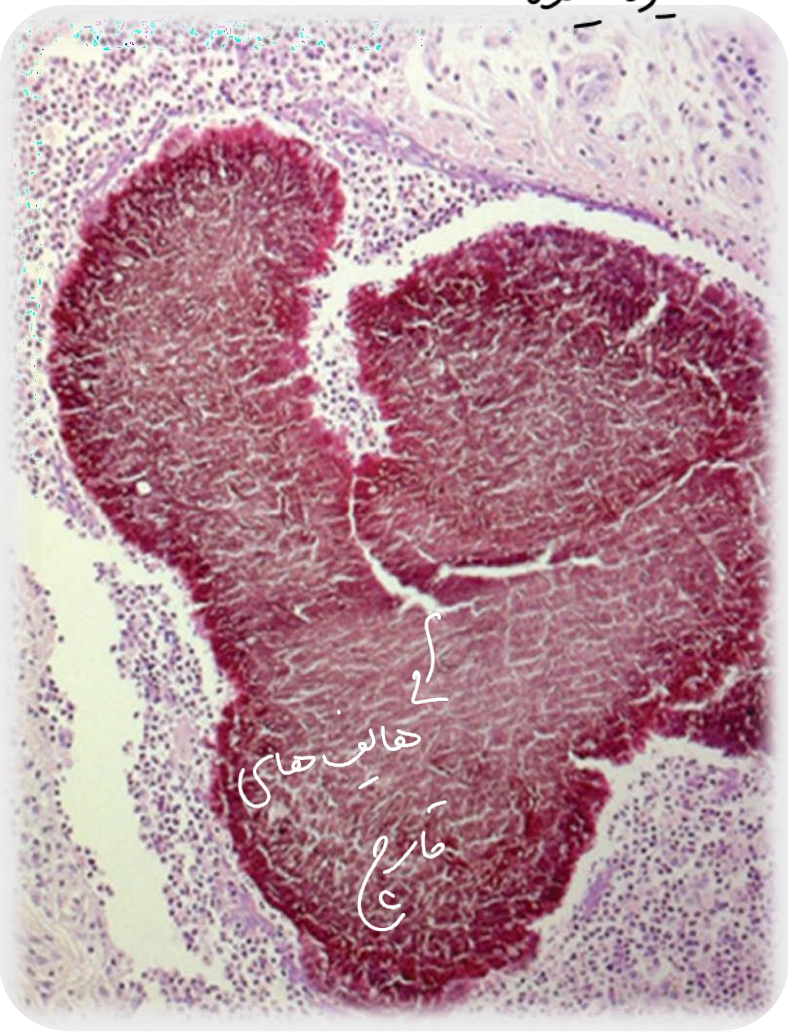

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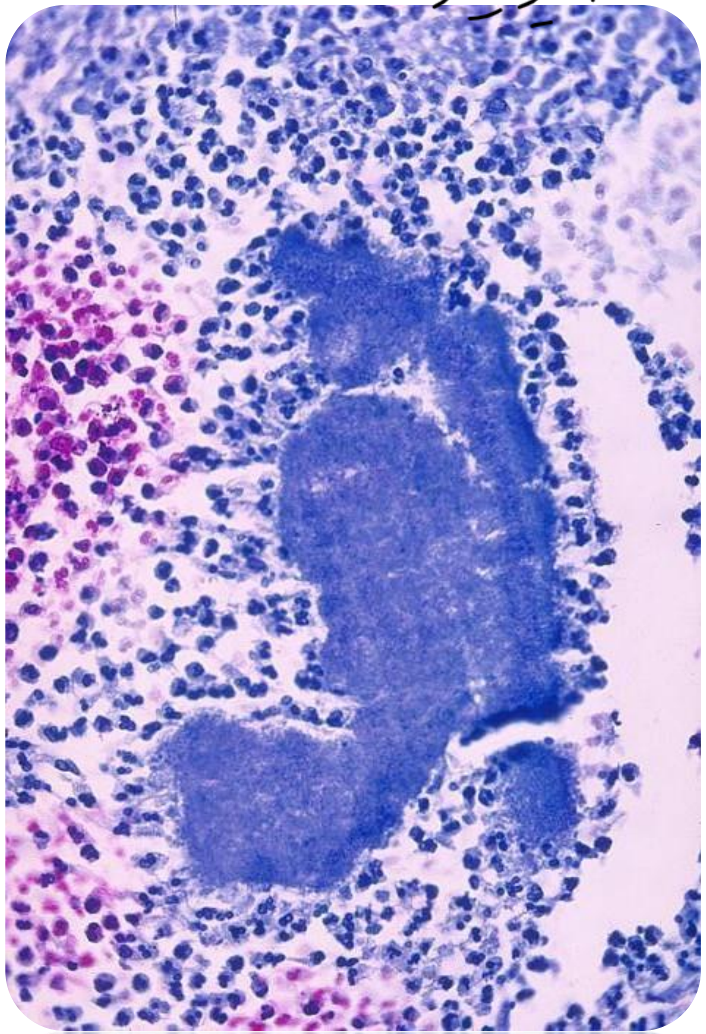


Culture:

❑ Actinomycetoma: ⟶

✓SDA, BHI

❑ Eumycetoma:

- Culture is essential for an etiologic diagnosis; however, performing cultures with eumycetoma specimens is laborious and complicated by a high rate of bacterial contamination.
- Before culture, grains should be washed several times with sterile saline solution to reduce bacterial and mold contamination, then crushed using sterile technique and plated on SDA containing chloramphenicol (SC).
- Medium containing cycloheximide should be avoided because it inhibits the growth of some eumycetoma agents, such as some *Fusarium* spp. and *Aspergillus* spp.
- Specimens should be incubated at both room temperature and 35°C for 6–8 weeks.

Imaging:

- All patients need **imaging studies** (X-ray or magnetic resonance scans) to determine the true extent of infection, which tends to involve bone in the later stages.

Serology:

- There is **no reliable** serologic test available for the diagnosis of eumycetoma.
- Serology is good for monitoring treatment.

- پاسخ آنتی صعیف
- رشد کند و مزمن ← واکنش سیستمی ضعیف
- تنوع عامل قارچی ← ست آنتی بادی اختصاصی برای هر عامل ضدی پیچیده و ناکارآمد

Treatment

- Usually, **actinomycetoma** responds better to treatment than eumycetoma.
- Generally, if bone is infected, the response to treatment is poor.

❑ Actinomycetoma:

✓ Cycles of the combination: amikacin sulfate 15 mg/kg twice daily for 3 weeks + cotrimoxazole 1.5 mg/kg twice daily for 5 weeks.

✓ Rifampicin/ Streptomycin/ tetracyclines

❑ Eumycetoma:

✓ Currently, there is no specific treatment or favorable prognosis for eumycetoma.

✓ Azole-class antifungal agents, such as itraconazole 400 mg/day and Ketoconazole 800 mg/day, for 6 months are commonly used.

✓ Surgical excision of newly formed lesions may help prevent the spread of infection; however, amputation may become necessary in advanced stages of the disease.

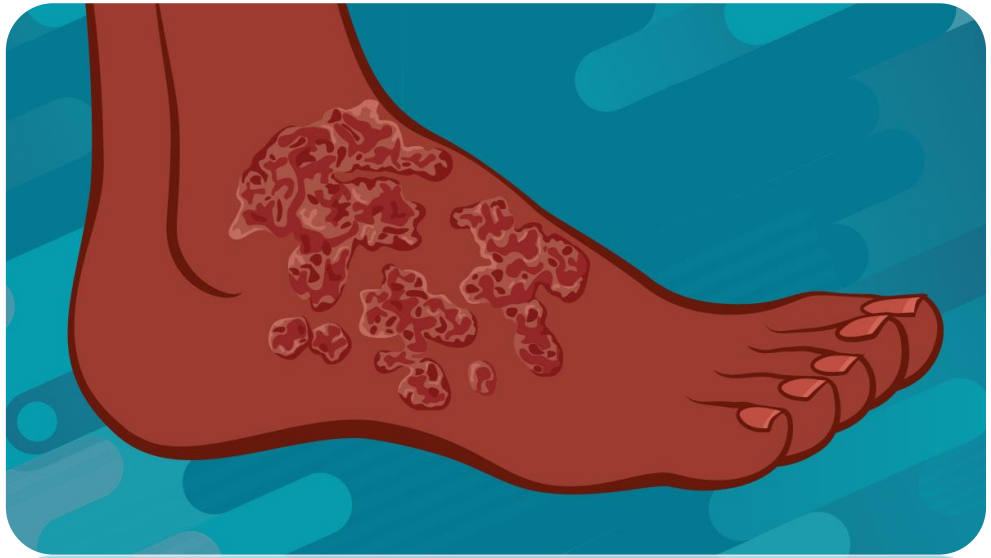
✓ Treatment duration is long, up to years.

Chromoblastomycosis (CBM)

- Chronic granulomatous and suppurative skin infection, which is classified as a subcutaneous mycosis caused by pigmented dematiaceous fungi.
- It was first reported in Brazil in 1914 by Max Rudolph, a German physician.

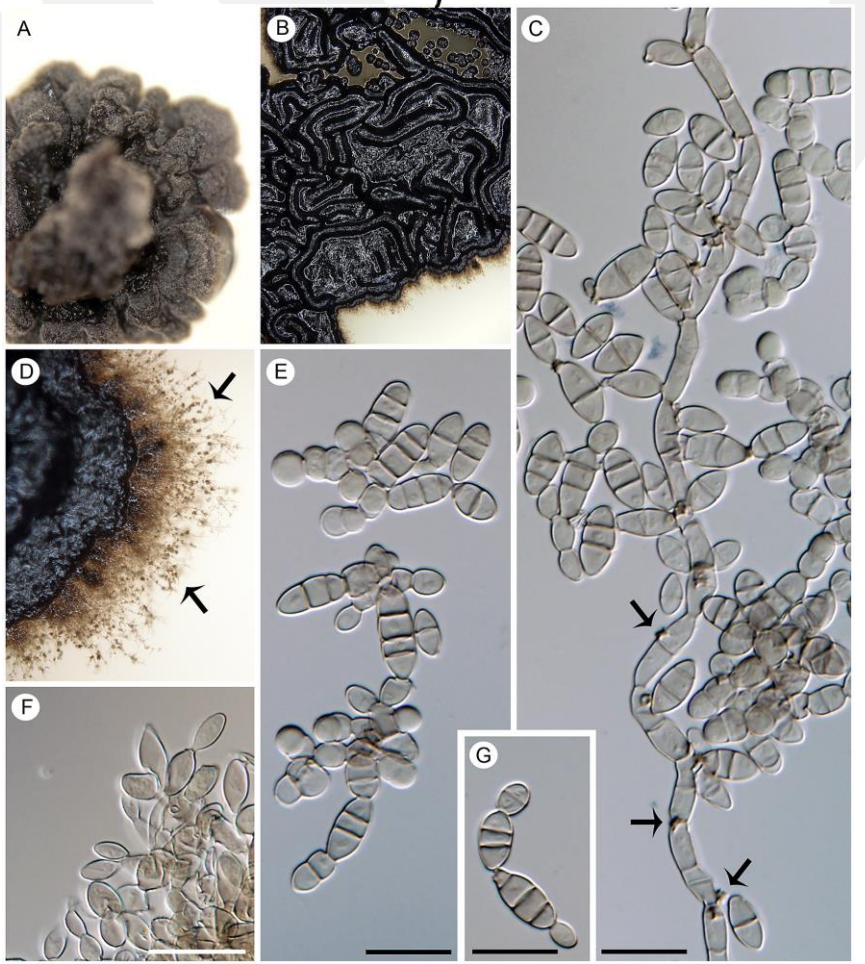
Histopathological aspects were first described by Medlar in 1915 (**Medlar bodies**).

- The usual clinical presentation is a slowly enlarging exophytic warty plaque with superficial crusting and black dots.

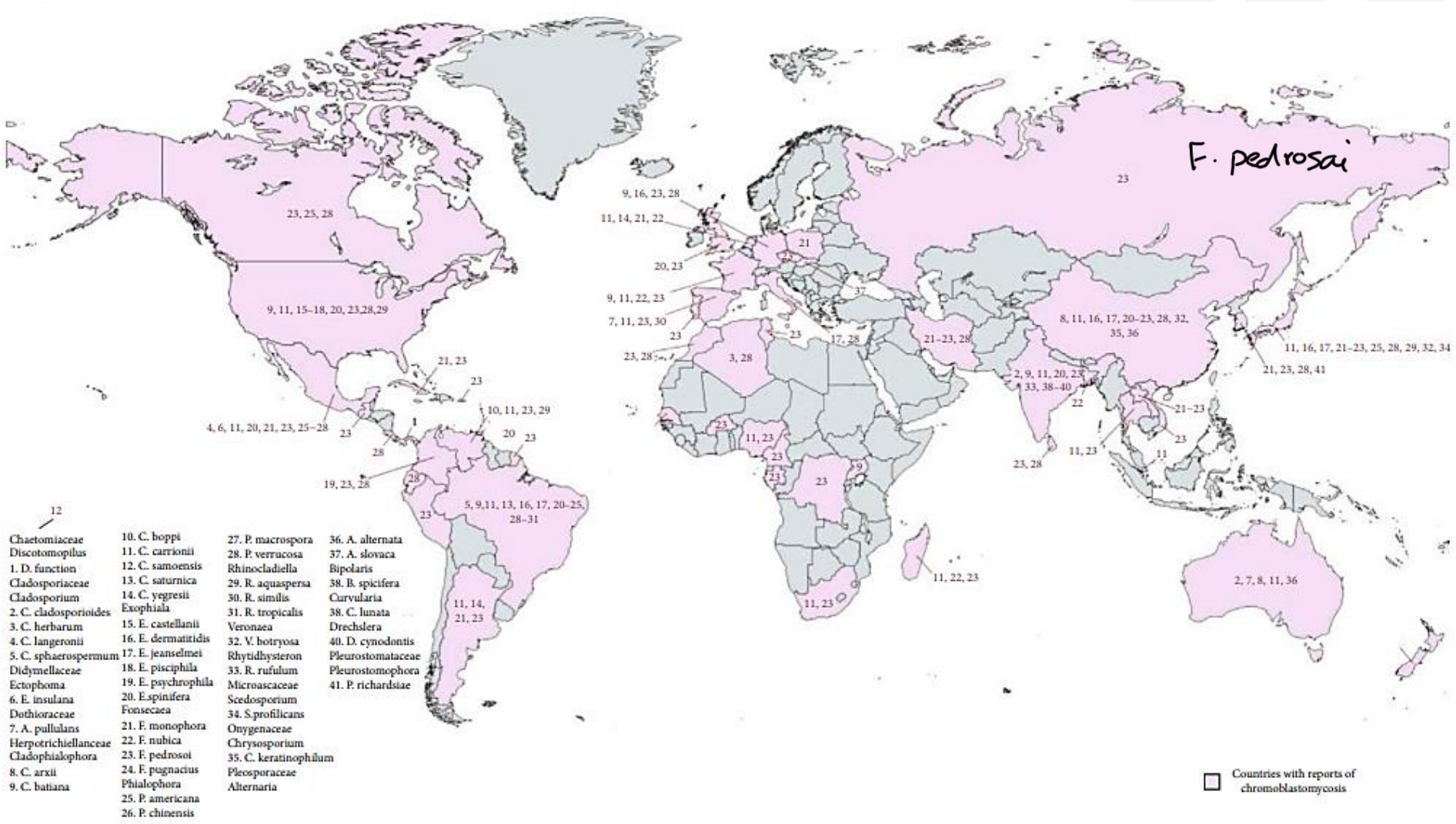


What fungi cause CBM?

- Dematiaceous fungi
- These melanized fungi are saprophytes and are found in soil, plants, woods, and organic materials in decomposition.
- The Herpotrichiellaceae family has the most clinical importance and includes the main genera that cause CBM: *Fonsecaea*, *Cladophialophora*, *Exophiala*, *Phialophora*, *Rhinocladiella*, and *Veronaea*.
- Last 10 years, most of the cases were caused by genera ***Fonsecaea*** and ***Cladophialophora***, and the most prevalent species infecting humans were ***F. pedrosoi***, ***F. monophora***, ***F. nubica***, and ***Cladophialophora carrionii***



Etiology


F. pedrosai
23, 25, 28
9, 11, 15–18, 20, 23,28,29
4, 6, 11, 20, 21, 23, 25–28
19, 23, 28
5, 9,11, 13, 16, 17, 20–25, 28–31
11, 14, 21, 23
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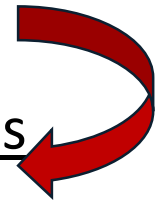
11, 22, 23
8, 11, 16, 17, 20–23, 28, 32, 35, 36
21–23, 28
2, 9, 11, 20, 23, 33, 38–40
23, 28
11, 23
11, 16, 17, 21–23, 25, 28, 29, 32, 34
21, 23, 28, 41
21–23
2, 7, 8, 11, 36
12
Chaetomiaceae
Discotomopilus
1. D. function
Cladosporiaceae
Cladosporium
2. C. cladosporioides
3. C. herbarum
4. C. langeronii
5. C. sphaerospermum
Didymellaceae
Ectophoma
6. E. insulana
Dothioraceae
7. A. pullulans
Herpotrichiellanceae
Cladophialophora
8. C. arxii
9. C. batiana
10. C. boppi
11. C. carrionii
12. C. samoensis
13. C. saturnica
14. C. yegresii
Exophiala
15. E. castellanii
16. E. dermatitidis
17. E. jeanselmei
18. E. pisciphila
19. E. psychrophila
20. E.spinifera
Fonsecaea
21. F. monophora
22. F. nubica
23. F. pedrosoi
24. F. pugnacius
Phialophora
25. P. americana
26. P. chinensis
27. P. macrospora
28. P. verrucosa
Rhinocladiella
29. R. aquaspersa
30. R. similis
31. R. tropicalis
Veronaea
32. V. botryosa
Rhytidhysteron
33. R. rufulum
Microascaceae
Scedosporium
34. S.profilicans
Onygenaceae
Chrysosporium
35. C. keratinophilum
Pleosporaceae
Alternaria
36. A. alternata
37. A. slovaca
Bipolaris
38. B. spicifera
Curvularia
38. C. lunata
Drechslera
40. D. cynodontis
Pleurostomataceae
Pleurostomophora
41. P. richardsiae
Countries with reports of chromoblastomycosis

Epidemiology

- In a traumatic event with such elements, hyphae can be inoculated through the skin, initiating the infection.
- CBM is considered an occupational disease, which occurs primarily among farm laborers, palm tree and babassu coconut harvesters, lumberjacks, and agricultural product traders.
- **Two important notes:**

1. Tropical countries, and people refuse to wear protective equipment during the day (shoes, gloves, garments, etc.)

2. low-income countries and sometimes live far away from medical services



- In 2017, CBM was added to the list of **NTD** the World Health Organization.

Epidemiology

- Common in tropical and subtropical countries; In the **African continent** (Madagascar, South Africa), in **Asia** (India, China, Japan, Australia), in **South America** (Brazil, Mexico, Venezuela) are the most important countries with the occurrence of CBM. In the USA and Europe, CBM is **rare**.
- Prevalent in **men**, between 30 and 50 years, working in agriculture.
- The lower extremities are the most affected area, followed by the arms and the cephalic segment.

Clinical Manifestations

- Lesions are usually **painless**, unless there are secondary bacterial infections.
- The initial lesion appears at the site of hyphae inoculation; however, some patients did not report traumatic lesions at the site of lesion development.
- Initially, an isolated **macular lesion** appears and evolves to an **erythematous papule**, which gradually increases in size and further develops into a **papulosquomous** form, sometimes with a polymorphic aspect that can be misdiagnosed with other skin diseases.
- Progressively, the lesions become the characteristic **verrucous** aspect. At the beginning of the disease, the lesions are asymptomatic and did not interfere with patient activities, but over time, patients reported itching, accompanied or not by pain.
- Fungi can spread through tissues by the lymphatic system.
- Infection may occur anywhere in the body, but if it starts in the lower limbs, the lesions tend to spread to the knee, thigh, or instep.

Clinical Manifestations

- CBM exhibits **five** different clinical forms:

1. Nodular
2. Tumoral type
3. Verrucous
4. Plaque → فقط یک تغییر رنگ
5. Cicatricial → معمولاً ضایعات زخمی و سوزنده

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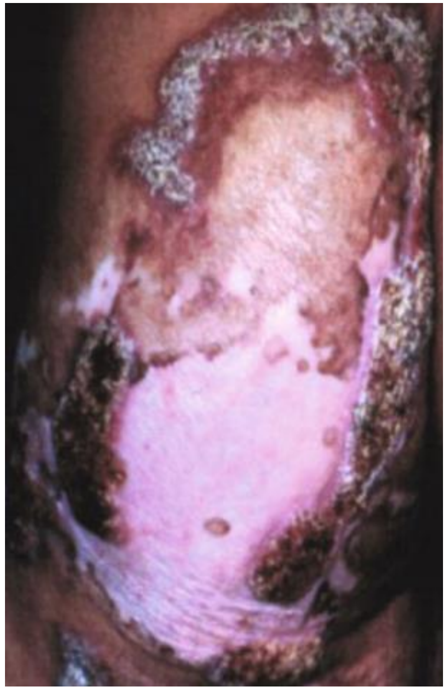

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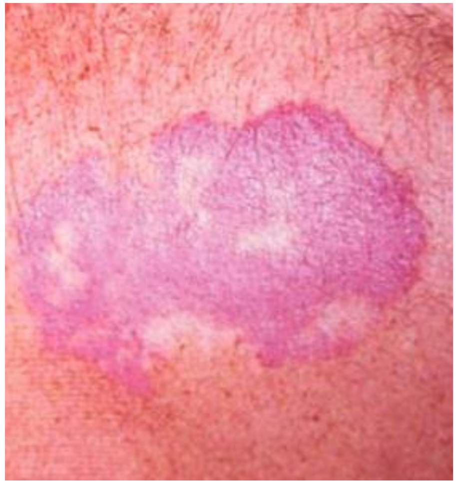

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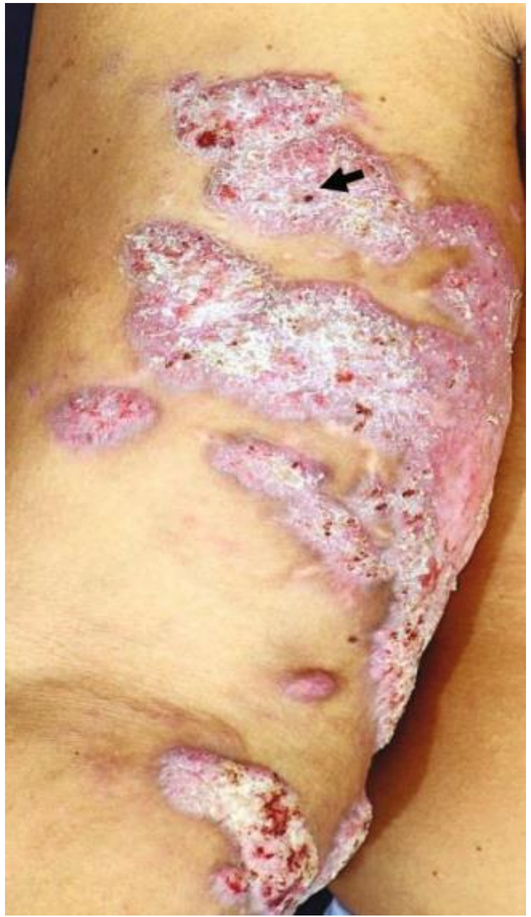

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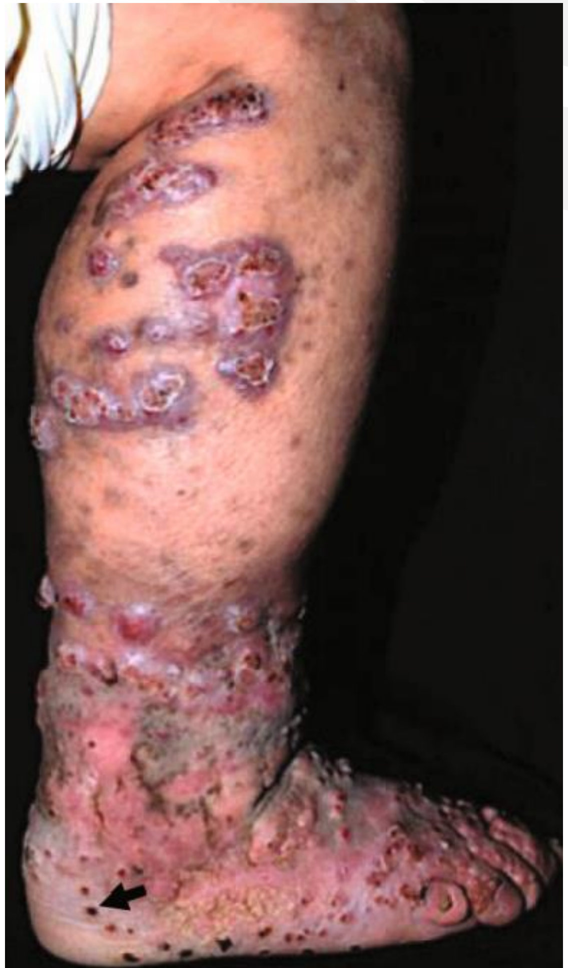

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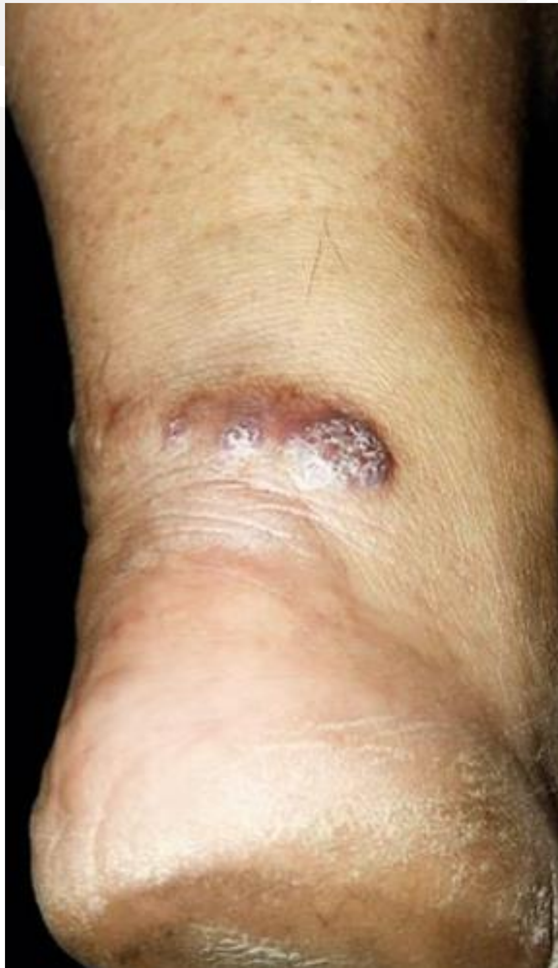
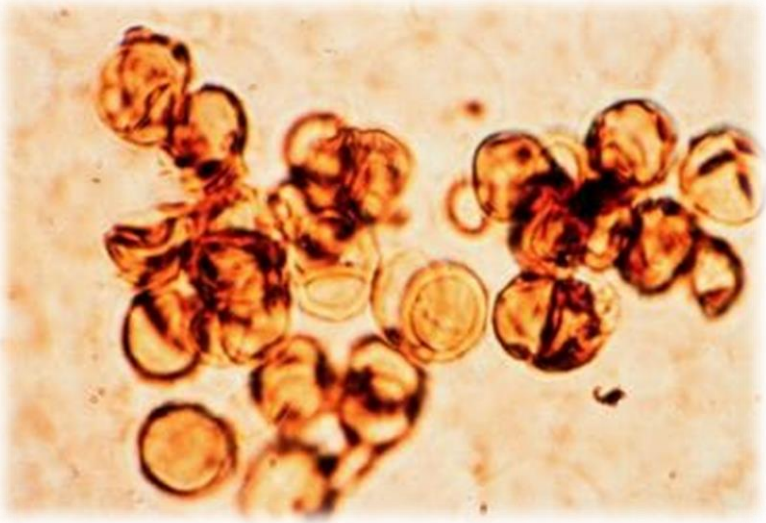


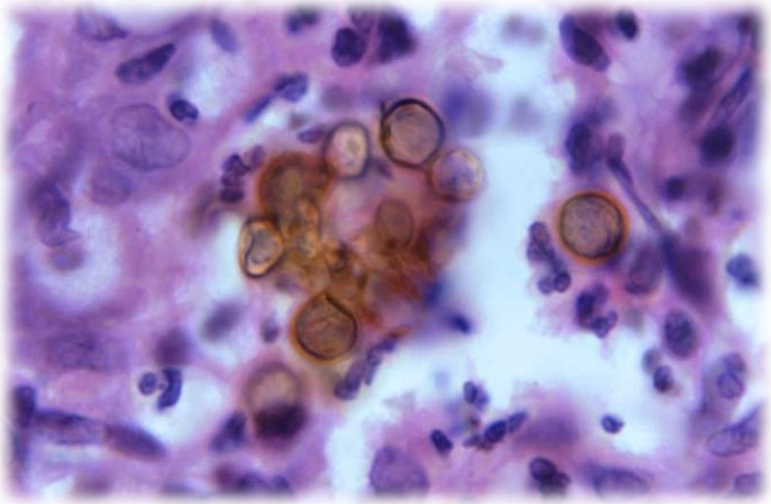
Diagnosis

- The diagnosis of CBM is based on clinical and epidemiological data.
- Direct mycological tests on skin scrapings containing crusts or biopsy, clarified by potassium hydroxide (10% KOH).

Examine specimens for muriform cells, which have 10 to 14 μm of diameter and exhibit a brownish color with a round-ellipsoid shape; they are crossed by transverse and longitudinal septa and show a thick cell wall.

Sclerotic bodies, Fumagoid bodies, Medlar bodies, Copper pennies





Diagnosis

- Histological sections

lymphohistiocytic inflammatory infiltrate characterized by the presence of granulomas, neutrophils, giant cells, plasma cells, and isolated or grouped muriform cells.

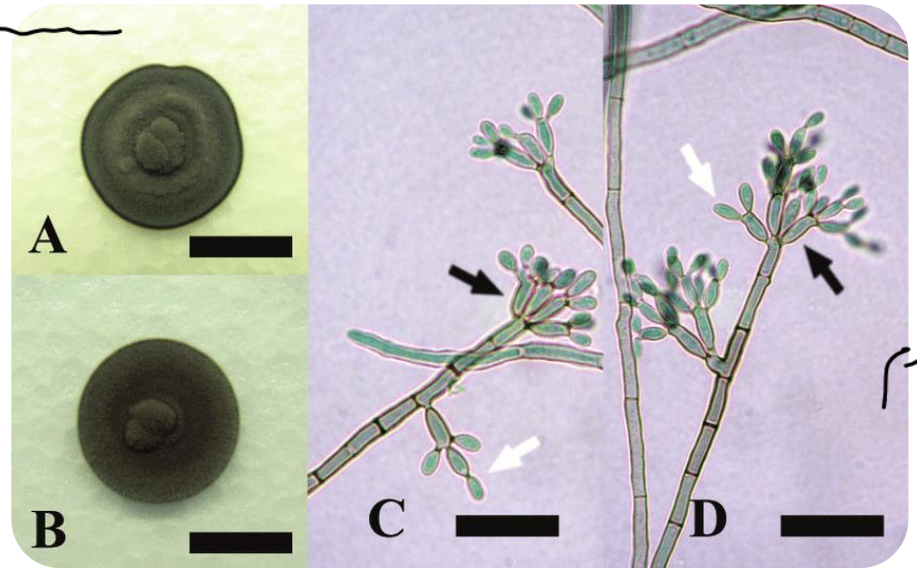
- Culture

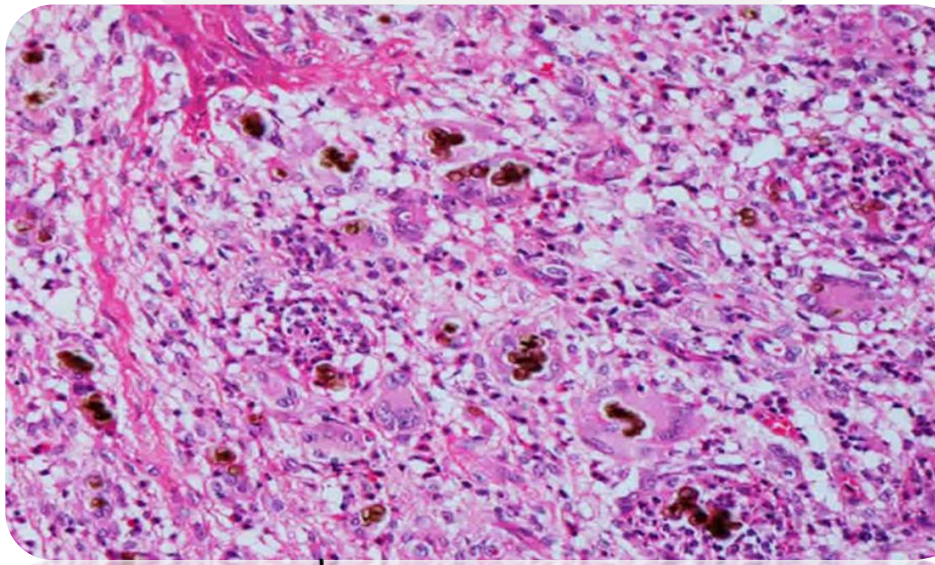
On SDA containing cycloheximide and chloramphenicol (SCC)

Very slow growing (4-6 weeks) / 25–30°C

- Serology

No commercial serologic tests





❑ Surgical excision:

✓ Cure chromoblastomycosis and is the treatment of choice for patients with **mild disease**.

✓ The excision should extend into the subcutis, and there should be at least a 0.5 cm margin of healthy-appearing skin at all margins.

❑ Antifungal drugs:

✓ Initiated for **moderate-to-severe** disease

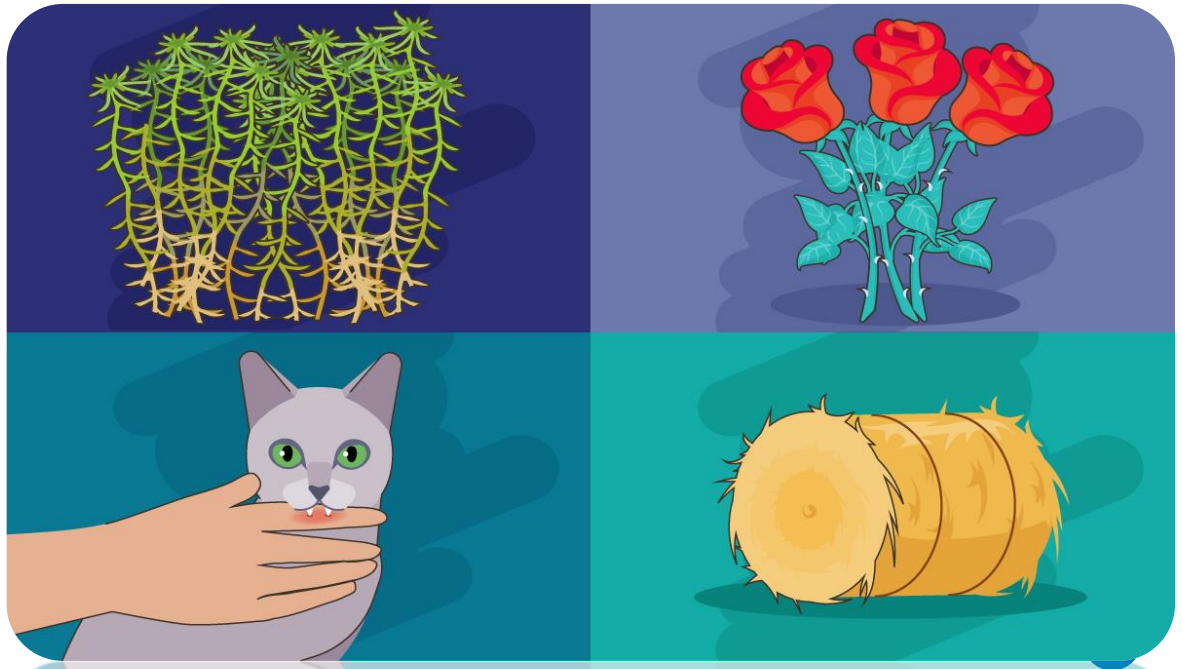
✓ The primary recommended treatments are terbinafine 250 to 500 mg/day and itraconazole 200 to 400 mg/day, administered on dual oral therapy.

✓ Other interventions, such as cryotherapy, heat therapy, and light-based therapies, may be useful as adjunctive treatments.

✓ Long-term follow-up is necessary to determine whether patients have achieved a cure.

Sporotrichosis

- Subacute to chronic infection caused by the dimorphic fungus *Sporothrix schenckii* and related species, which are found worldwide in vegetation, decaying organic matter, Sphagnum moss, and soil.
- *Sporothrix schenckii* was first isolated in 1896 by Benjamin Schenx, a medical student at Johns Hopkins Hospital.
- The classical transmission route refers to sapronosis.
- Infection usually involves cutaneous and subcutaneous tissues but can occasionally occur in other sites.



What fungi cause Sporotrichosis?

- Dimorphic ***Sporothrix*** genus

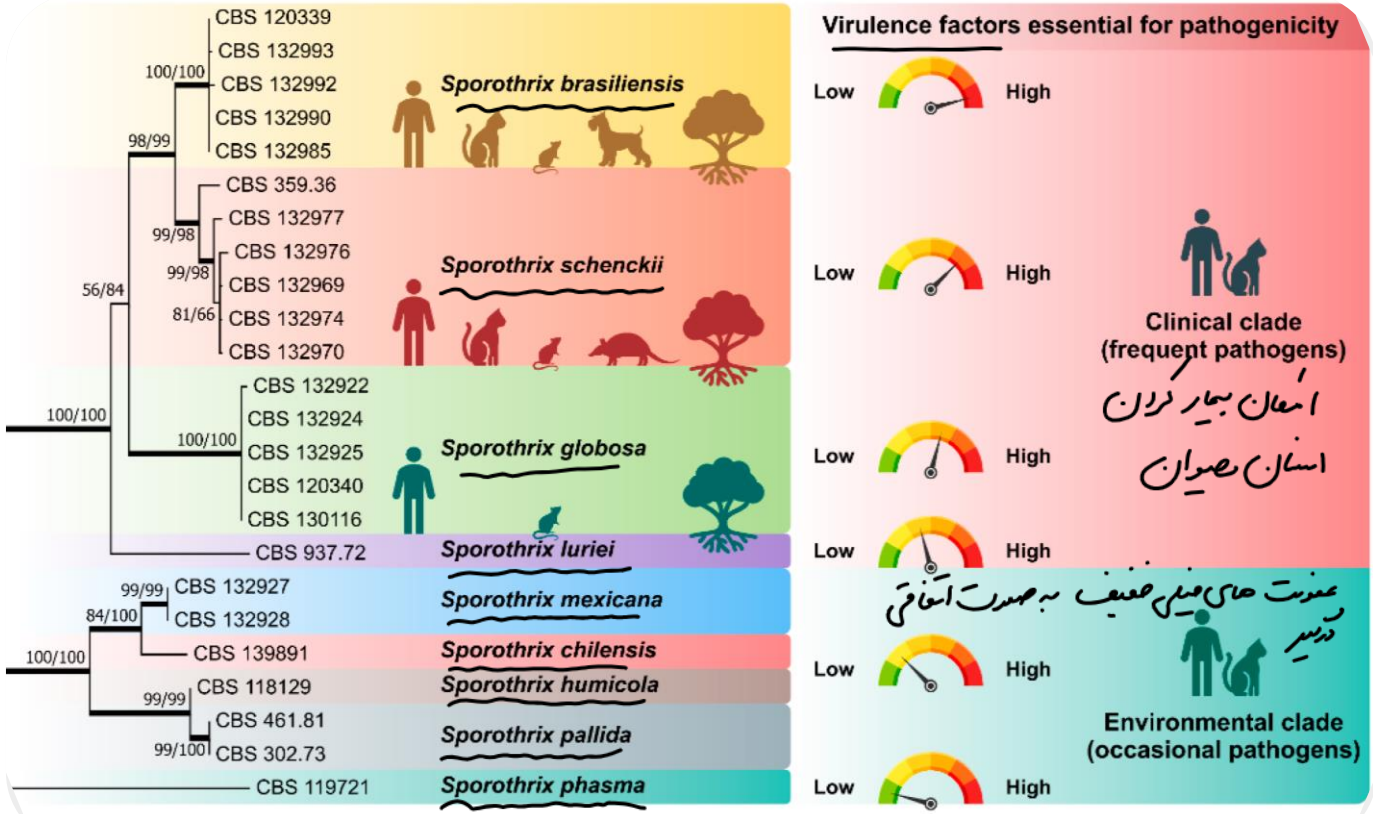
❑In the clinical:

S. brasiliensis is highly virulent for the warm-blooded vertebrate host, followed by *S. schenckii*, *S. globosa*, and *S. luriei*.

❑In the environmental:

S. chilensis, *S. humicola*, *S. mexicana*, and *S. pallida* are occasional pathogens with mild-pathogenic potential to mammals.

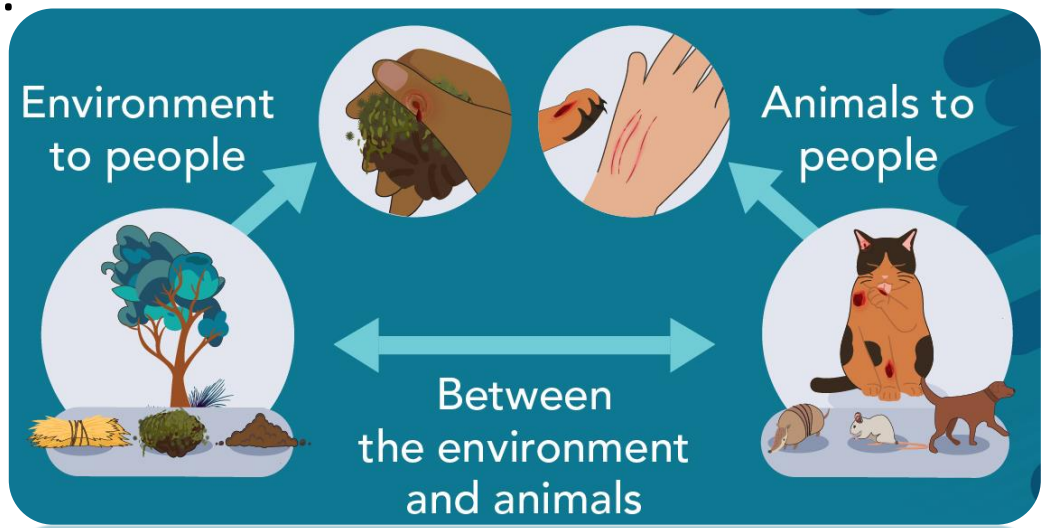
- *Sporothrix phasma*, a species with no virulence to mammals.



Epidemiology

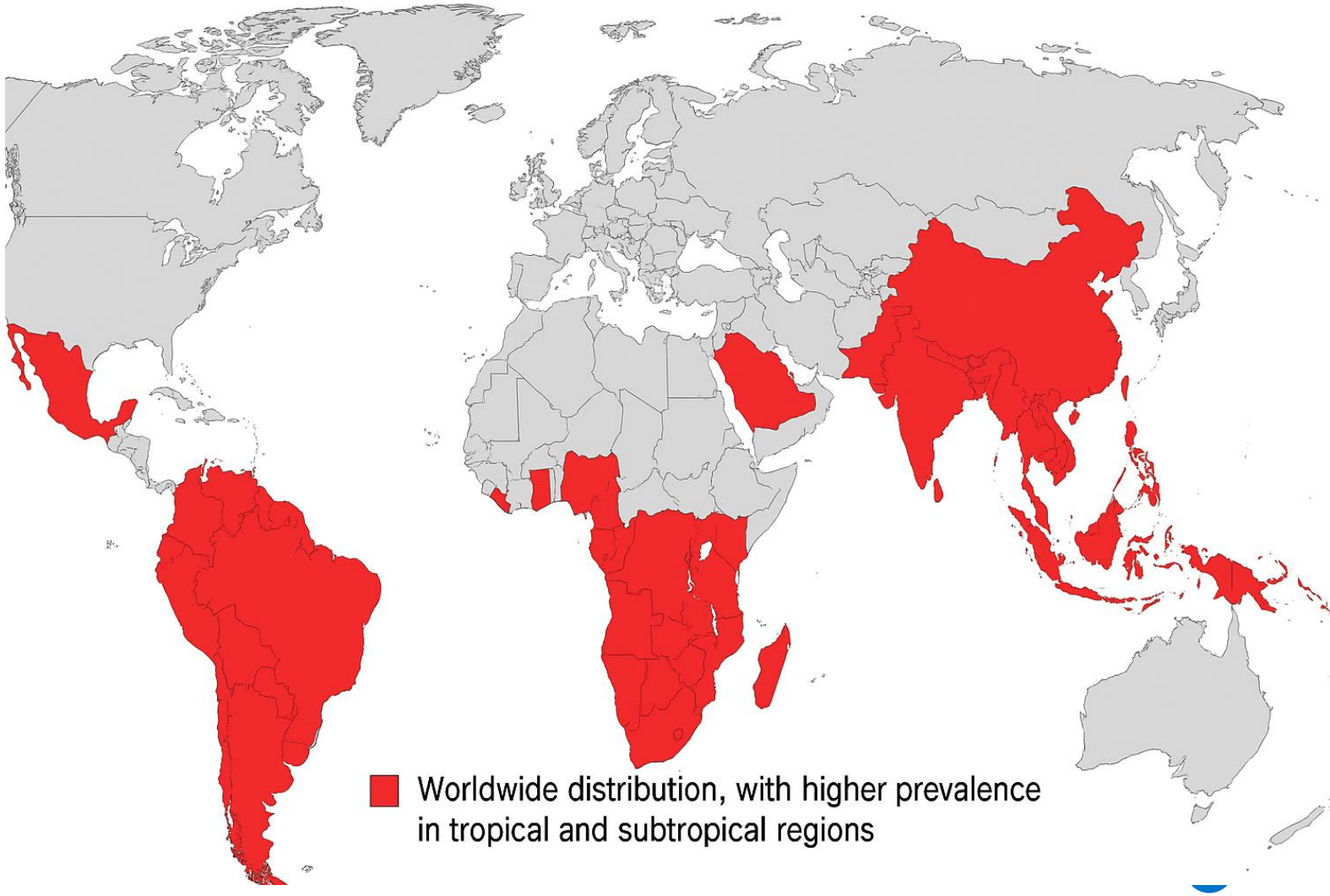
- Globally distributed but predominates in tropical and subtropical regions.
- Classical route via traumatic inoculation from contaminated plant material, soil, or organic matter (e.g., thorns, splinters).
- Less commonly, infection occurs via inhalation of conidia, leading to pulmonary sporotrichosis
- Cat-to-human transmission (zoonotic transmission) is a major driver of recent epidemics in South America. (*Sporothrix brasiliensis*)
- Occupational/recreational exposures: rose gardeners, agricultural workers, forestry workers, miners (exposure to wood, soil, plant matter).

- Close contact with infected cats' important risk in zoonotic outbreaks.
- Immunosuppressed patients can develop more severe or disseminated disease.



Epidemiology

- **South America:** Brazil (hyperendemic, especially urban zoonotic outbreaks), Argentina, Colombia, Peru, Mexico.
- **Central America & Caribbean:** Sporadic cases reported in Panama, Guatemala, and the Dominican Republic.
- **Asia:** China, India, Japan, Malaysia, Thailand, South Korea.
- **Africa:** South Africa, Madagascar, Zimbabwe (environmental cases).
- **North America:** United States (mostly sporadic sapronotic cases, e.g., gardeners, forestry workers).
- **Europe:** rare; mainly imported or travel-related cases (Spain, Portugal, UK).



Lymphocutaneous Sporotrichosis

Clinical Manifestations

Rose Gardener's Disease → باغبانی صل رز

- Most common presentation.
- Initial lesion: painless papule or nodule at the site of inoculation.
- Progression to ulcerated nodules along lymphatic channels ("sporotrichoid spread")
- Usually on hands, arms, or legs.
- No systemic symptoms in immunocompetent hosts.
- Lesions ulcerate and discharge a serohemorrhagic exudate.

سرم + خون

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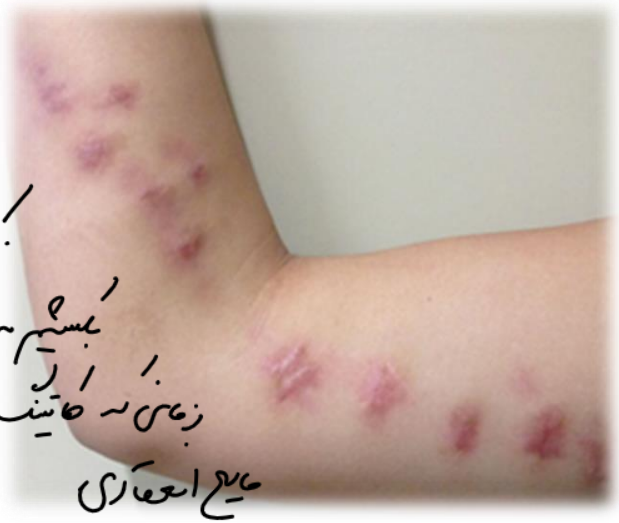
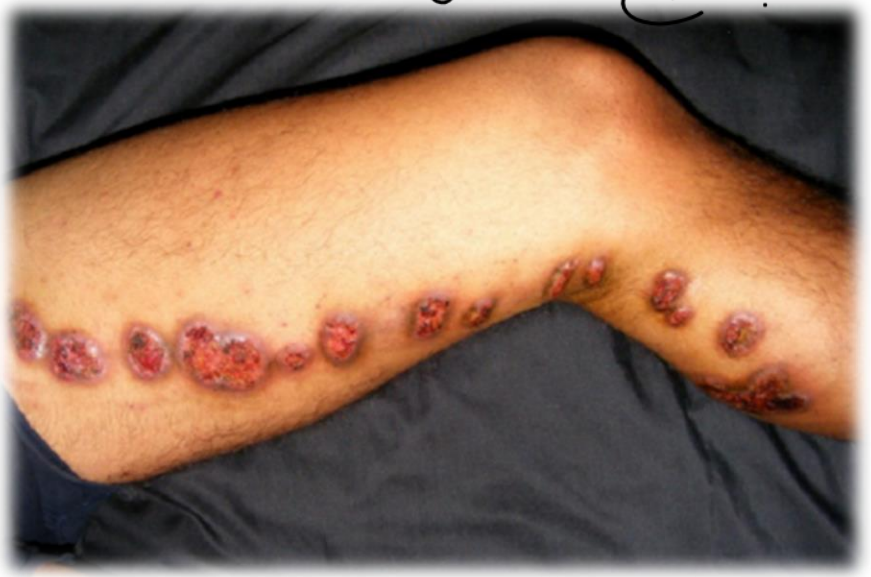
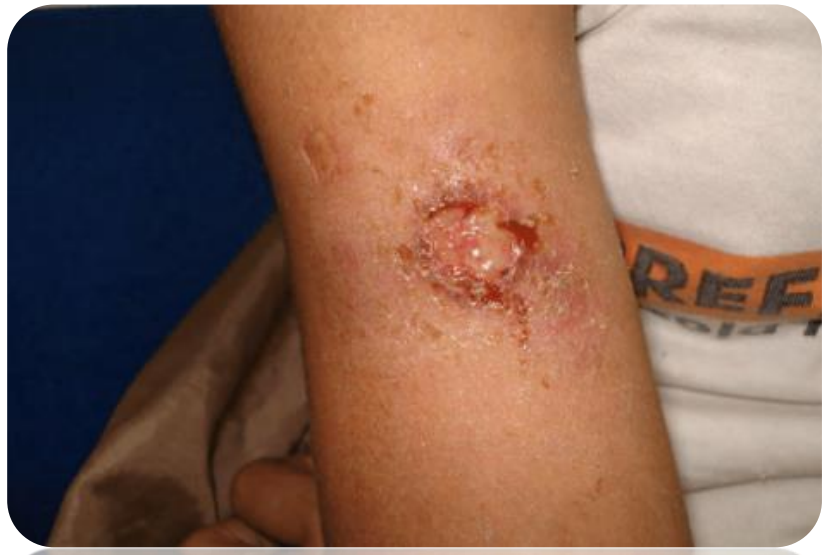


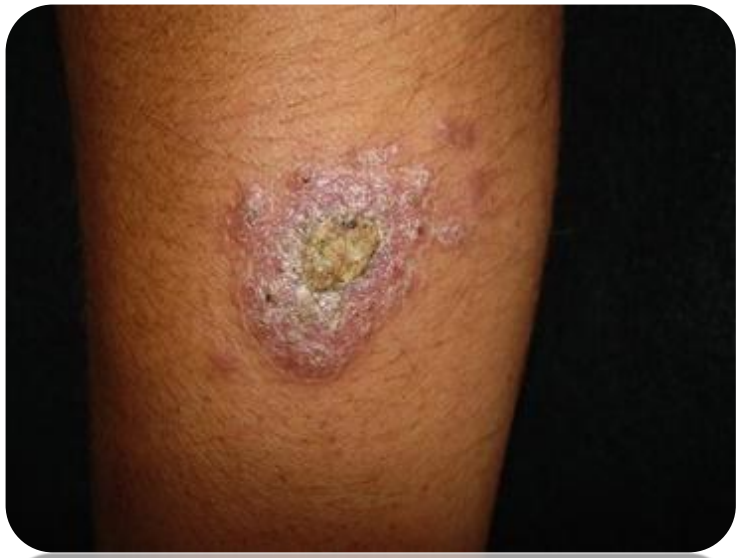


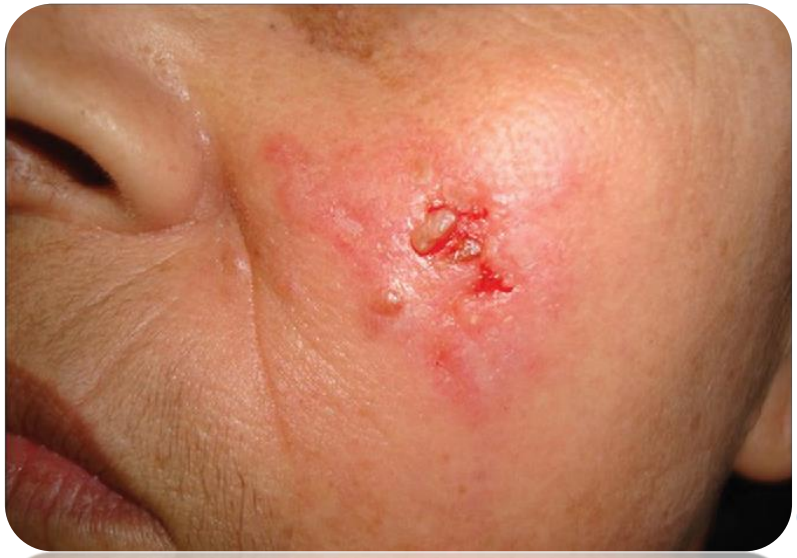
Fixed Cutaneous Sporotrichosis

Clinical Manifestations

- Single localized lesion at the site of inoculation.
- Lesion: verrucous plaque or ulcer, does not spread along lymphatics.
- Common in endemic areas (Latin America, Africa, Iran!)
- Mainly the limbs, hands, and fingers.
- Discharging a serous or purulent fluid.
- Often mistaken for cutaneous leishmaniasis or chromoblastomycosis



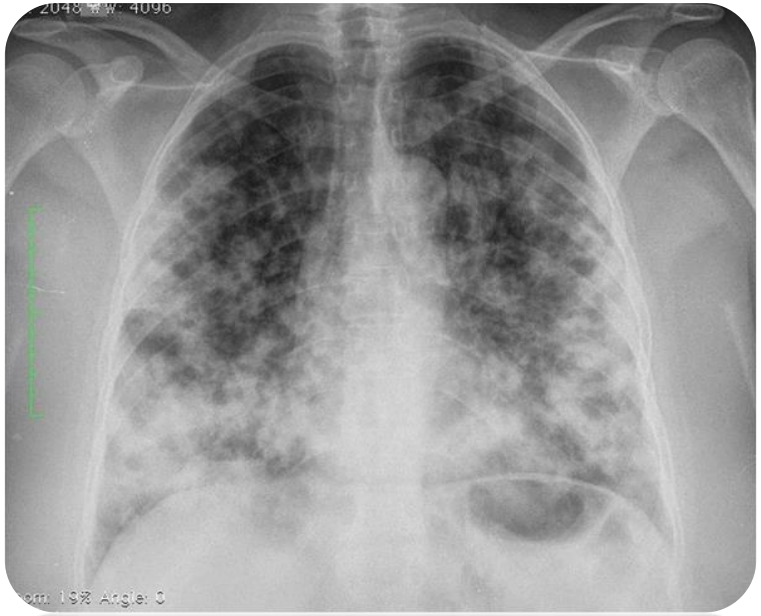


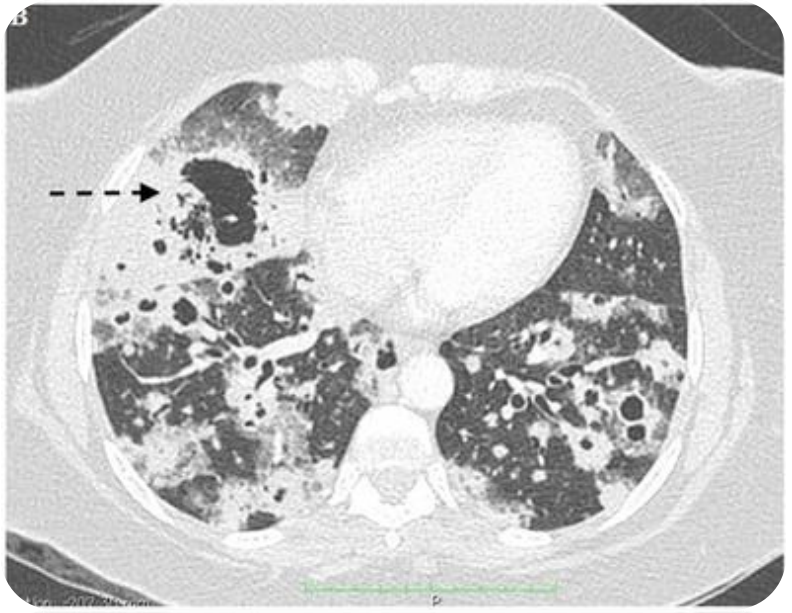


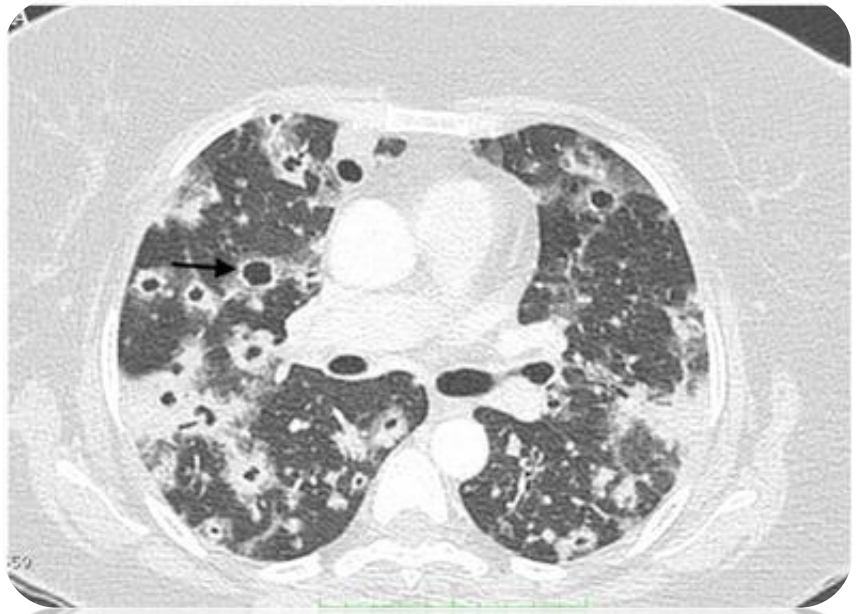
Pulmonary Sporotrichosis

Clinical Manifestations

- Rare form, usually in patients with chronic lung disease or alcoholism
- Caused by inhalation of conidia.
- Clinical features: chronic cough, hemoptysis, weight loss
- Radiology: fibronodular or cavitary lesions, mimicking TB



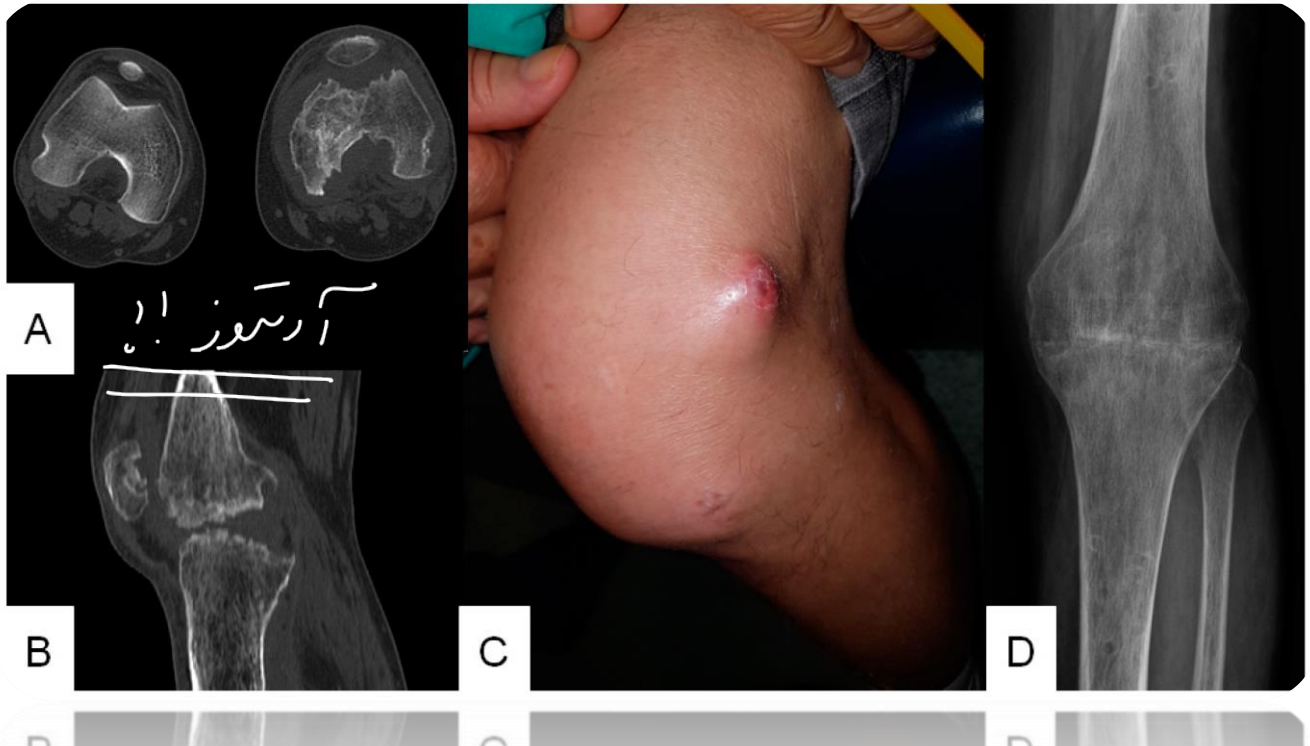


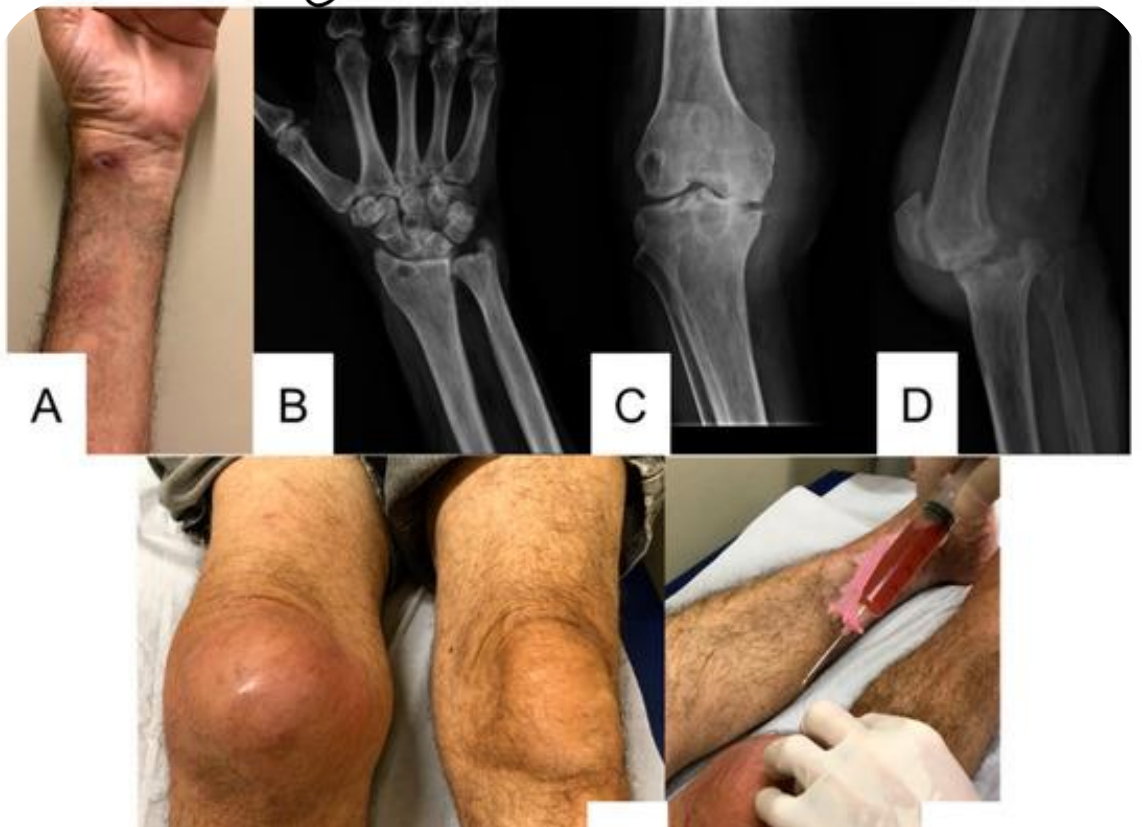


Osteoarticular Sporotrichosis

Clinical Manifestations

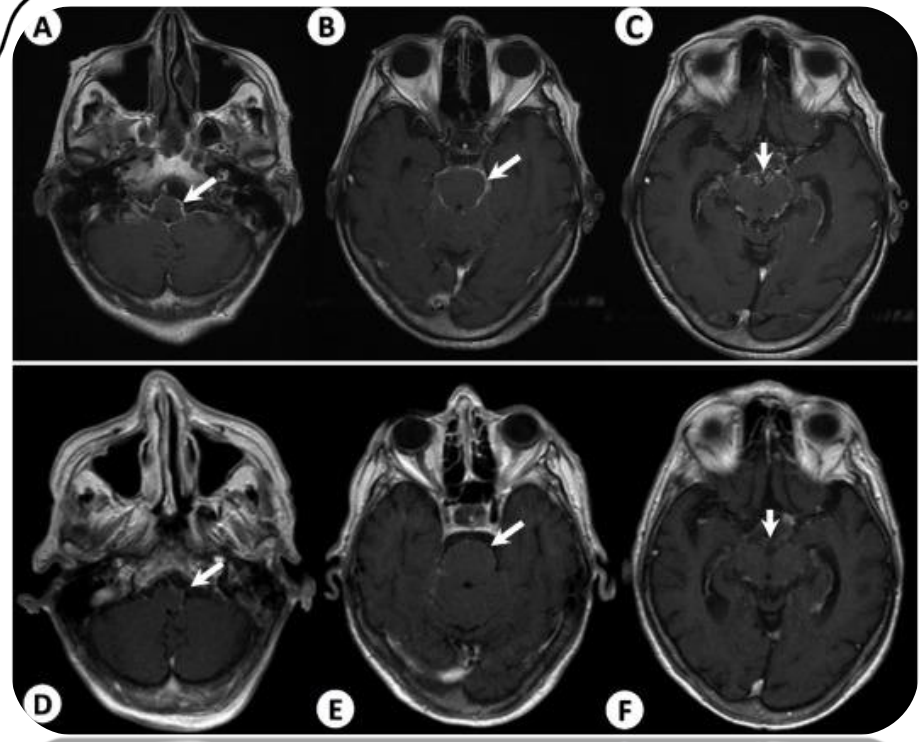
- Subacute or chronic infection of joints and bones
- Most commonly knee, elbow, wrist.
- Clinical signs: chronic monoarthritis, swelling, pain, limited motion
- Often misdiagnosed as tuberculous arthritis. → معمولا تشخیص اش mis می شه

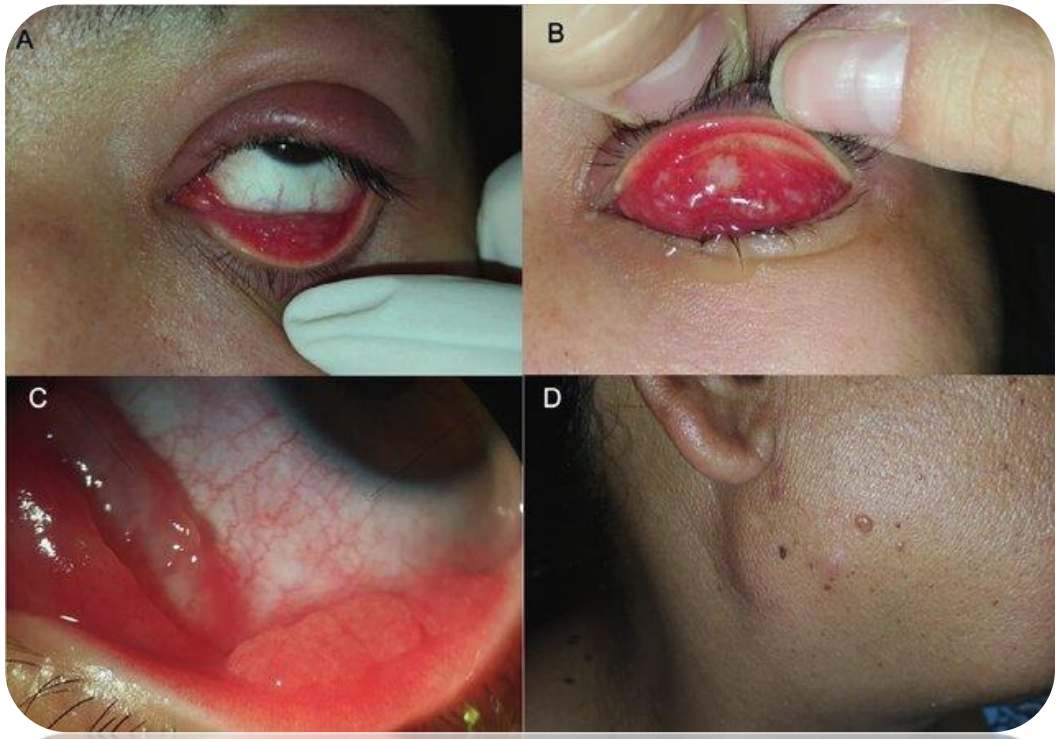




Disseminated Sporotrichosis

- Uncommon; occurs in immunocompromised patients (HIV, transplant, steroids).
- Multi-organ involvement: skin, lungs, CNS, bones, eyes.
- May present with systemic symptoms (fever, weight loss, sepsis-like picture).
- Very high morbidity and mortality without treatment.





Diagnosis

1.Clinical material:

Tissue Biopsy: From skin lesions, nodules, or ulcers. **Aspirate:** From pus or synovial fluid.

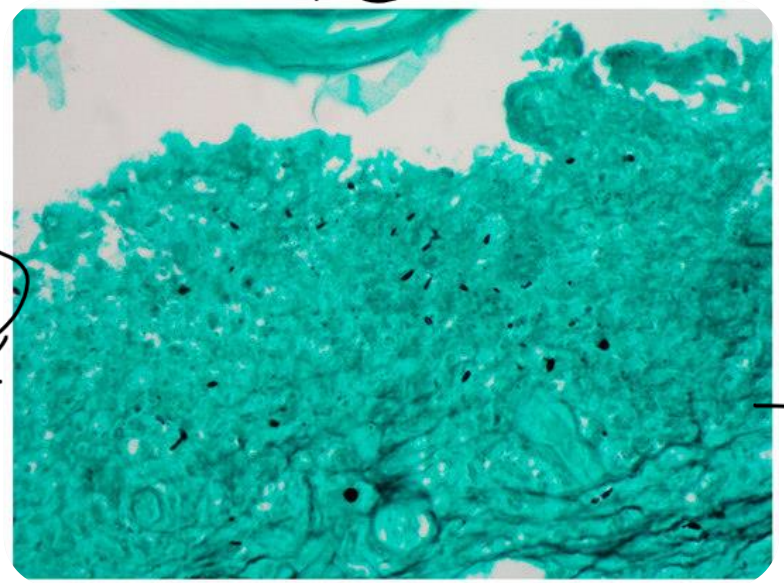
Sputum/BAL: For pulmonary cases.

2. Direct Microscopy:

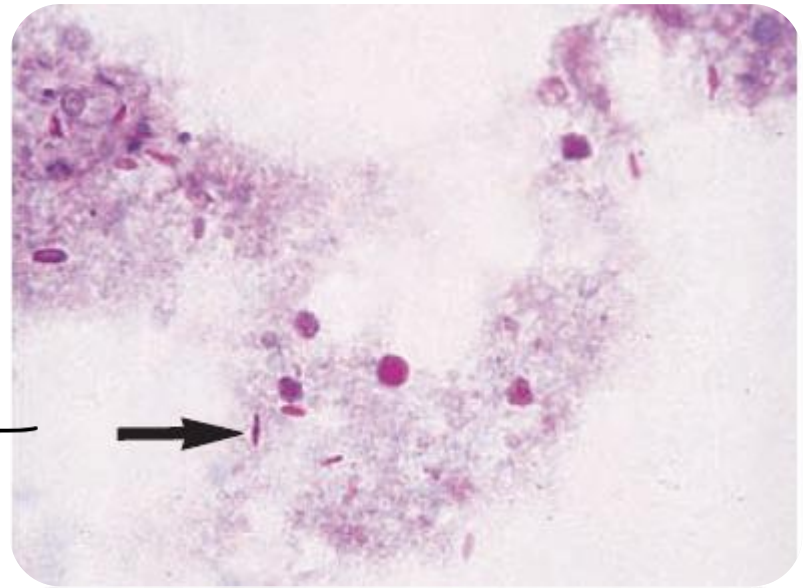
Using 10% KOH or common stains (Methylene blue, Gram).

Examine specimens for **oval, cigar-shaped, or budding yeast cells (3-5 µm in size).**

The yeast form is rarely seen in clinical specimens.



GMS



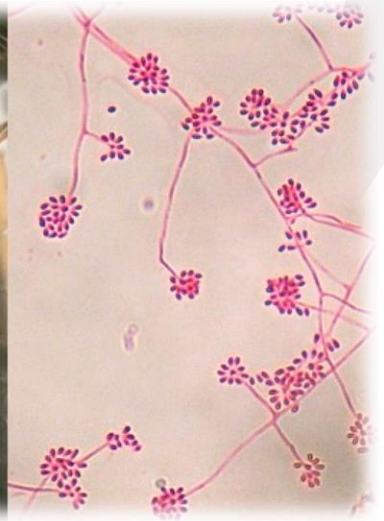
PAS

3. Culture (The Gold Standard)

Media: SDA or Mycosel/Mycobiotic Agar.

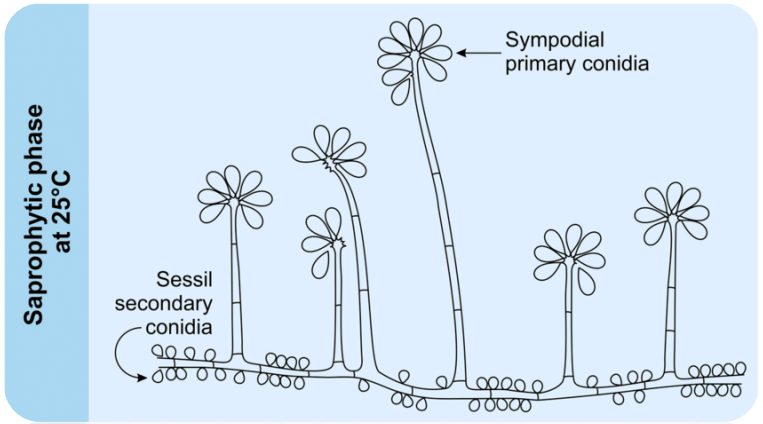
❑ Hyphal Phase

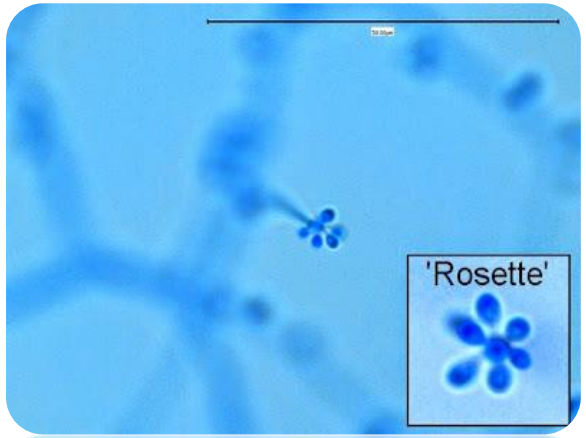
25-30°C: Optimal for mycelial (mold) form growth.

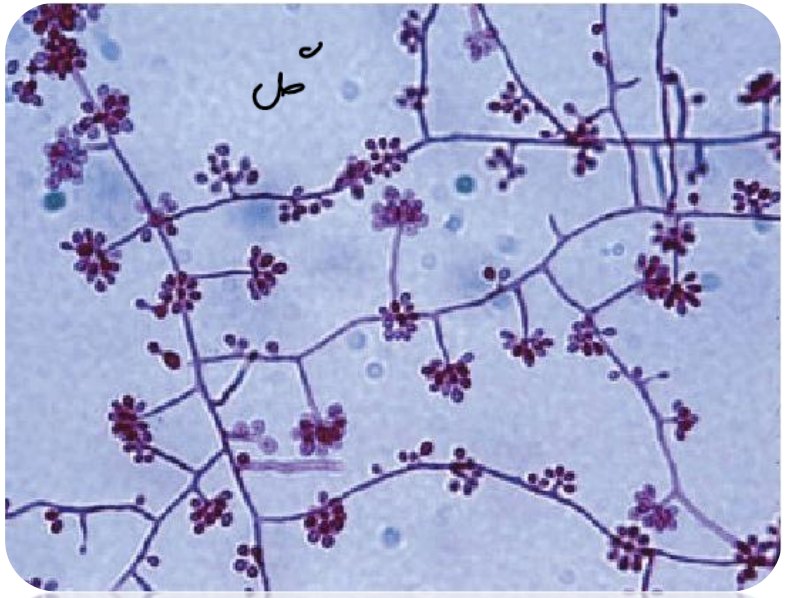


Appearance: Initially creamy, becoming leathery and wrinkled. Color changes from white/cream to dark brown or black with age.

Microscopy: Demonstrates delicate, septate hyphae with conidia in a "rosette" pattern or along the hyphae ("sleeve" pattern).





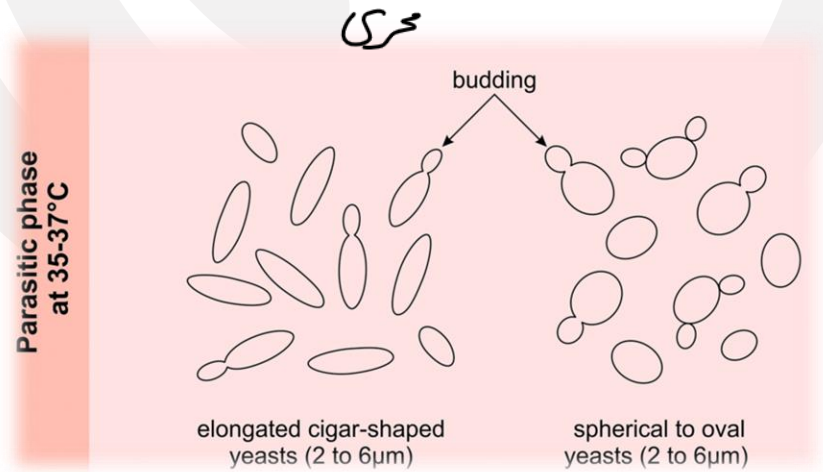


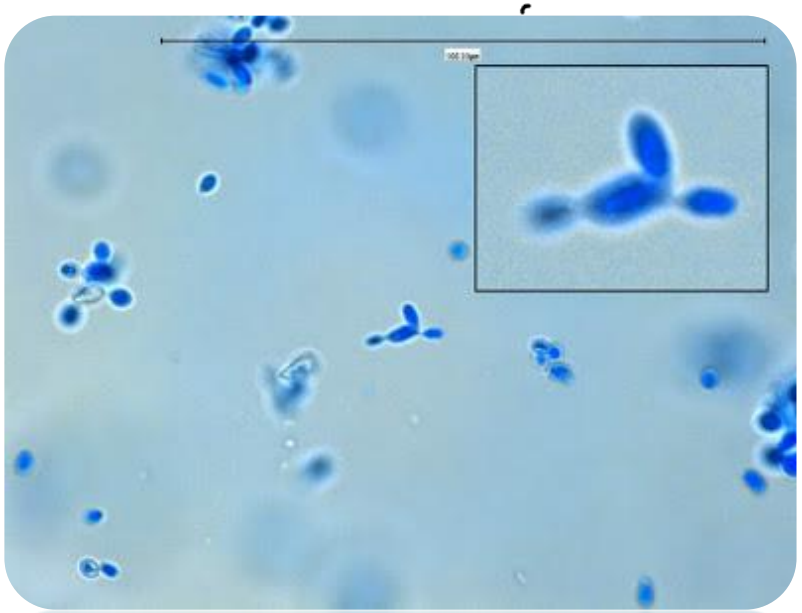
3. Culture (The Gold Standard)

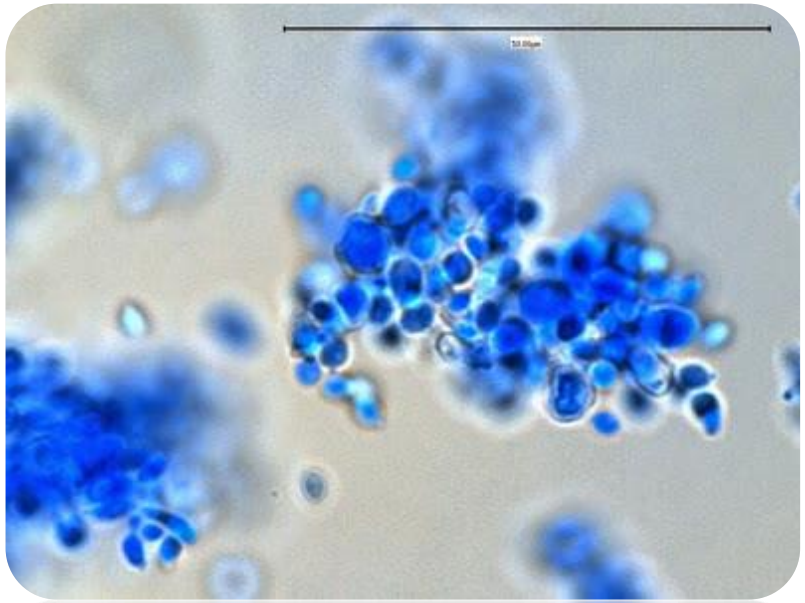
Yeast Phase ⟶ حتما مایه زنی بایه ای باشه

37°C (on enriched media like BHI Agar): Converts the mold to the yeast form. This temperature-dependent dimorphism is a key diagnostic feature.

Time to Growth: Typically, 3 to 5 days, but can take up to 2 weeks.





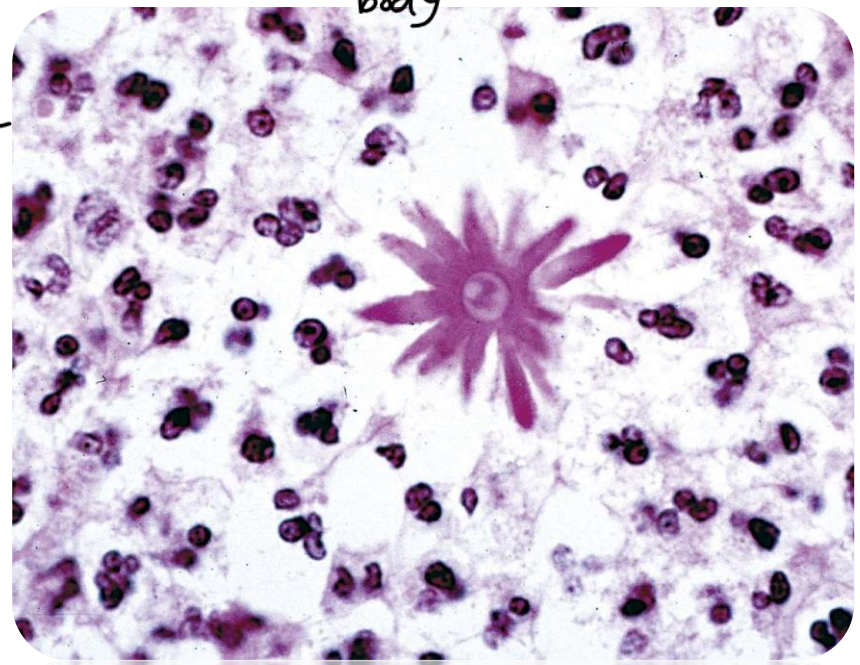


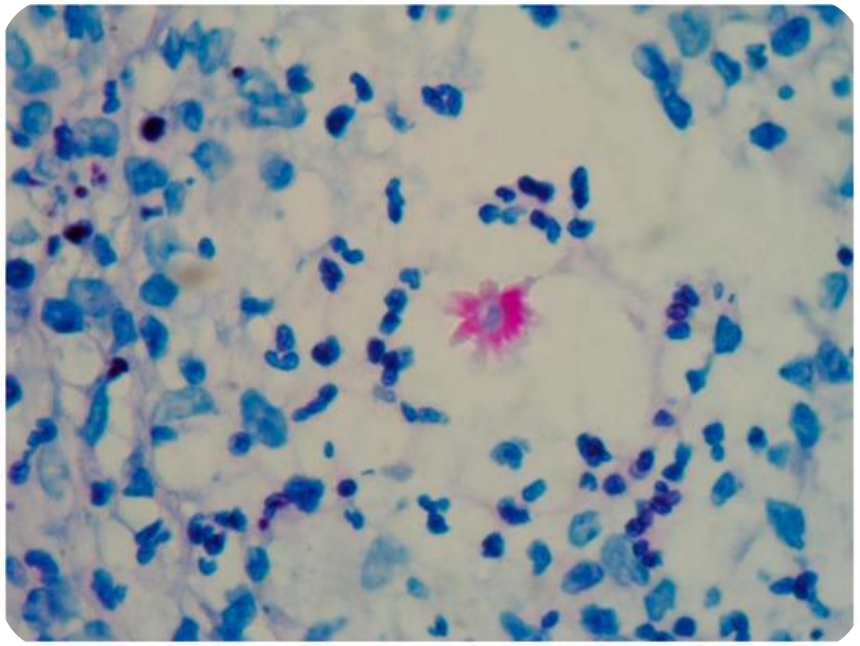
4. Histopathology

Stain: Hematoxylin and Eosin (H&E), Periodic acid–Schiff (PAS), Gomori methenamine silver (GMS).

Finding: Often shows a mixed pyogranulomatous inflammatory reaction.

Challenge: Yeast cells are sparse and difficult to find. The **asteroid body** (a yeast cell surrounded by eosinophilic splendor-like material) is a classic but infrequent finding.





5. Serology

Useful for extracutaneous and disseminated forms where culture is challenging.

Test: ELISA or Latex Agglutination for antibody detection.

- **Utility:**

High sensitivity for articular and disseminated disease.

Low sensitivity for cutaneous disease (often false-negative).

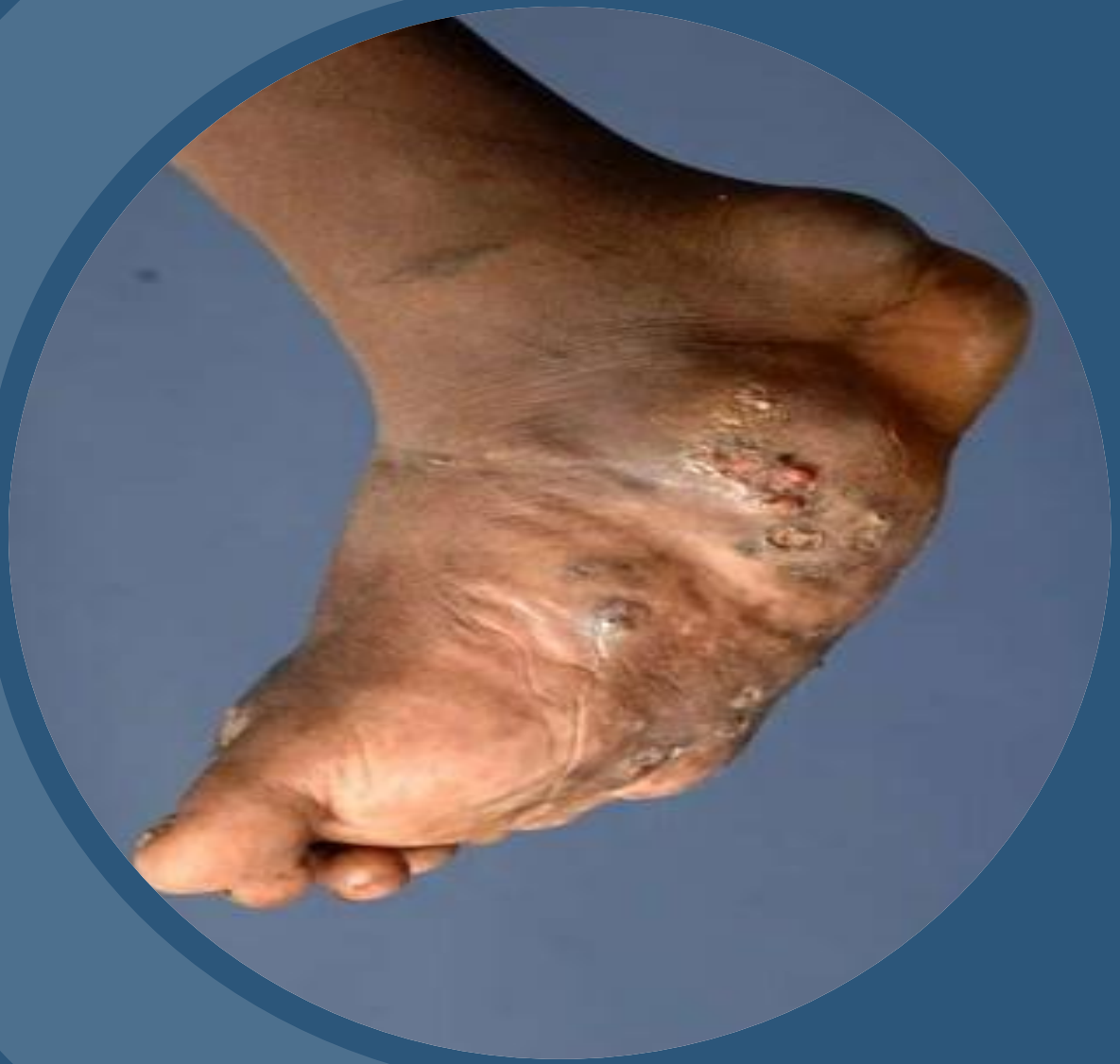
A positive result supports the diagnosis, especially in endemic areas.

Limitation: Can cross-react with other fungi (e.g., *Histoplasma*).

Treatment

Clinical Form	First-Line Treatment	Alternative / Step-Down Therapy	Duration
Lymphocutaneous /Cutaneous	Itraconazole 100-200 mg orally, once or twice daily.	Saturated Solution of Potassium Iodide (SSKI), Terbinafine, Fluconazole, Thermotherapy	3-6 months
Osteoarticular	Itraconazole 200 mg orally, twice daily.	Liposomal AmB (severe cases)	12-24 months
Pulmonary	Itraconazole 200 mg orally, twice daily (mild) Liposomal AmB 3-5 mg/kg IV daily (severe)	Surgery (for localized disease)	≥12 months
Disseminated	Liposomal AmB 3-5 mg/kg IV daily.	Itraconazole	≥12 months (often lifelong in immunocompromised)
Pregnancy	Local Thermotherapy	Amphotericin B (if severe, with caution)	As needed / Until delivery

Crucial Monitoring Note: When using **Itraconazole**, therapeutic drug monitoring is strongly recommended. Check serum levels after 2 weeks to ensure adequate absorption (target trough level: **>1.0 µg/mL**).



THANK YOU