EUMYCETOMA

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- Mycetoma is a chronic subcutaneous infection that develops after one of the multiple etiologic microorganisms is inoculated into a site of skin trauma.
- Although mycetoma is primarily a subcutaneous disease, it can involve bone and lymph nodes by contiguous spread.
- 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 can be caused by a variety of fungal agents (eumycetoma), or filamentous gram-positive branching bacteria belonging to the aerobic Actinomycetales (actinomycetoma).

ORGANISM

- The predominant human pathogens worldwide are:

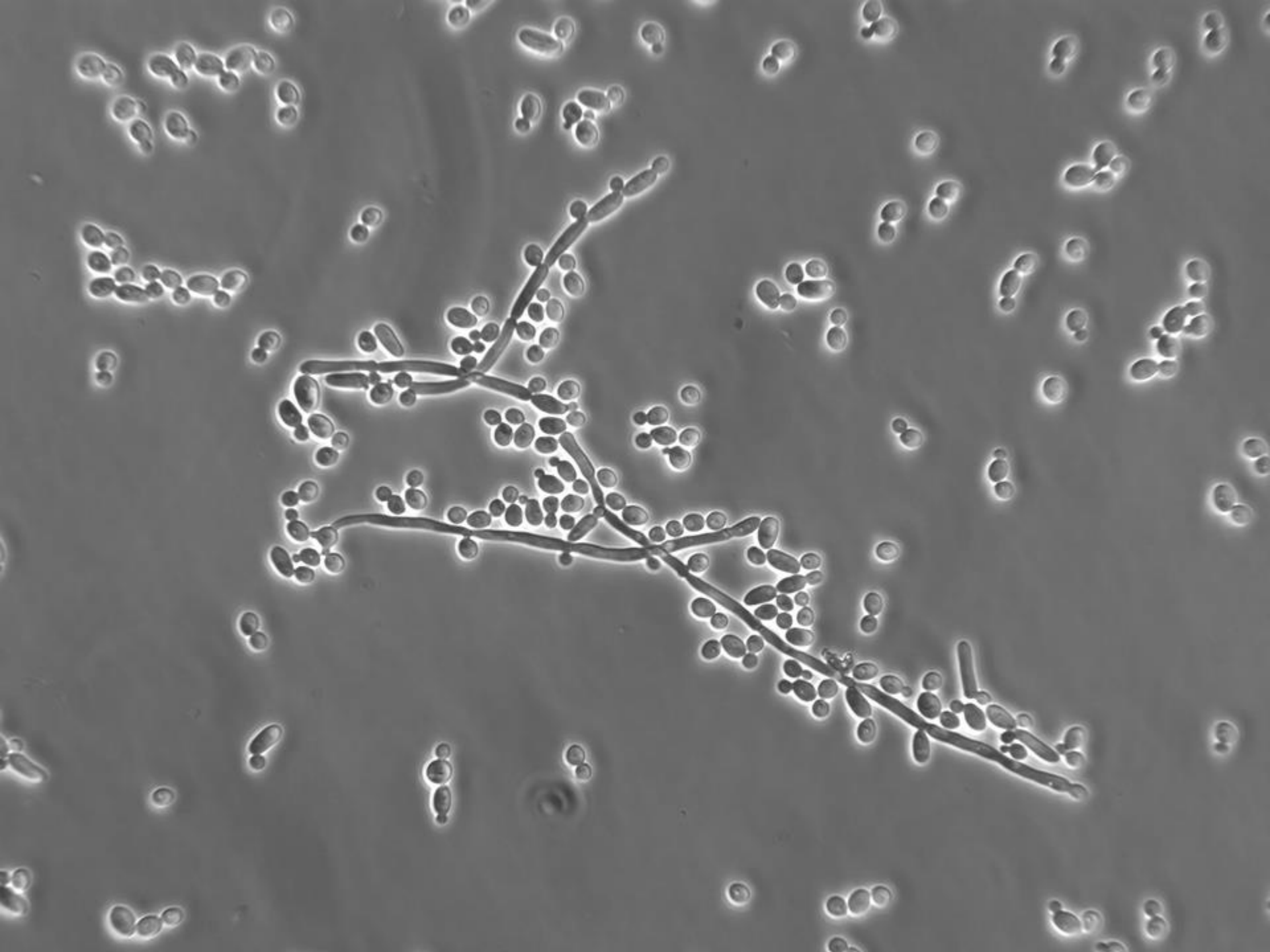
➢ *Madurella mycetomatis*

➢ *Pseudallescheria boydii/Scedesporium apiospermum,*

➢ *Leptosphaeria senegalensis,*

➢ *Madurella grisea.*

- These four fungi account for approximately 95% of eumycetoma cases.



PATHOGENESIS

- Disease usually develops as a result of minor trauma that inoculates contaminated material, usually soil, into the skin or subcutaneous tissue.
- After inoculation, a poorly defined host response precludes the development of free fungal filaments in the infected tissue, and instead leads to the development of the characteristic grain.
- Neutrophil-mediated tissue reaction leads to partial grain disintegration, but most of the grain remains and perpetuates a chronic inflammatory response.
- Macrophages and multinucleated giant cells clear dead neutrophils and grain fragments, and an epithelioid granuloma develops.

- The role of melanin that is present in variable amounts in grains from certain organisms, such as *M. mycetomatis*, is not completely understood.
- Melanin has been linked to virulence and pathogenicity, and it is considered the most important component of the grain cement.
- Melanin strengthens the grain and protects fungal cells from antibodies, hydrolytic enzymes, strong oxidants, and azole antifungal agents.

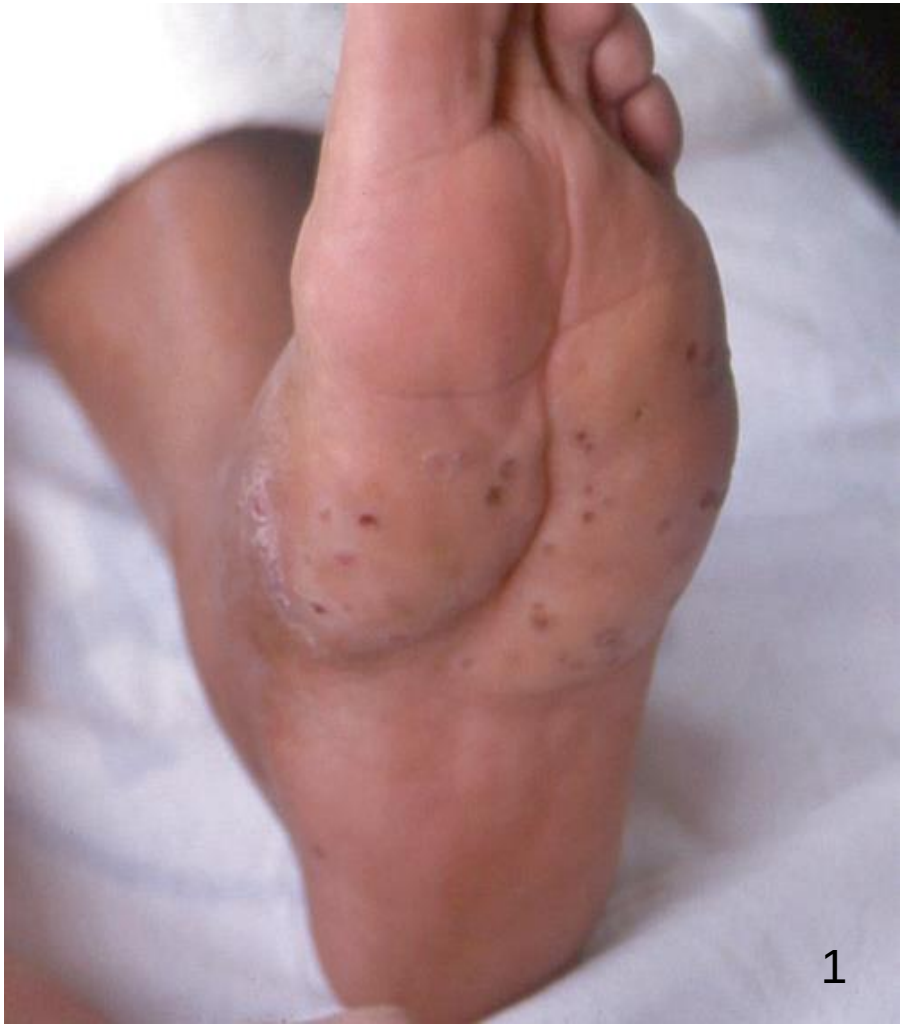
CLINICAL MANIFESTATIONS

- Eumycetoma principally affects otherwise normal men living and working in rural areas.
- The male-to-female ratio ranges between 3:1 and 5:1; the age at the time of diagnosis ranges from 3 to 77 years (mean 32.6 years). The average duration of symptoms ranges between 7.7 and 9.8 years, ranging from 1 month to 25 years.
- Most patients with eumycetoma are not classically immunocompromised, although diabetes is a frequent comorbidity.
- Eumycetoma has been reported in patients receiving chronic immunosuppressive therapy for renal and heart transplantation, leukemia, and idiopathic CD4 lymphopenia.
- Eumycetoma has not been reported in an HIV-infected patient.

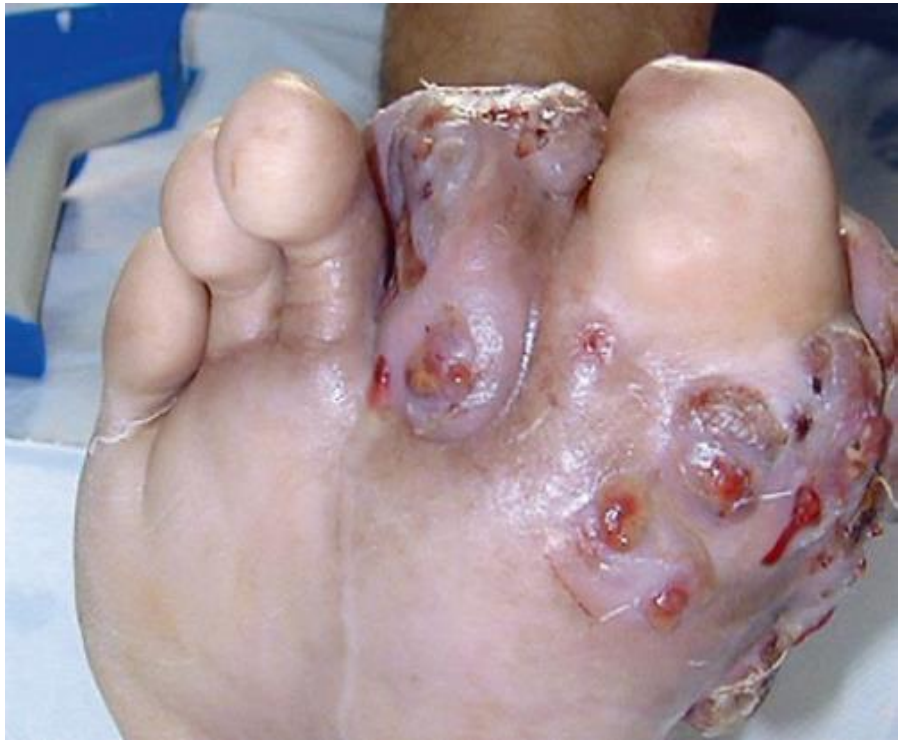
- Clinical characteristics and evolution of eumycetoma lesions are independent of the etiologic fungus; the clinical course depends on the anatomic location, duration of lesions, and medical intervention.
- Lesions begin as small, firm, painless, indurated subcutaneous nodules or plaques that gradually increase in size.
- The clinical course is somewhat slower for eumycetoma than for actinomycetoma.

- Initially, the lesion is well demarcated and may be encapsulated, especially when *M. mycetomatis* is the etiologic agent.
- The disease usually runs a chronic course from several years to decades, with lesions spreading slowly to adjacent structures by contiguous spread, and virtually never by hematogenous dissemination.

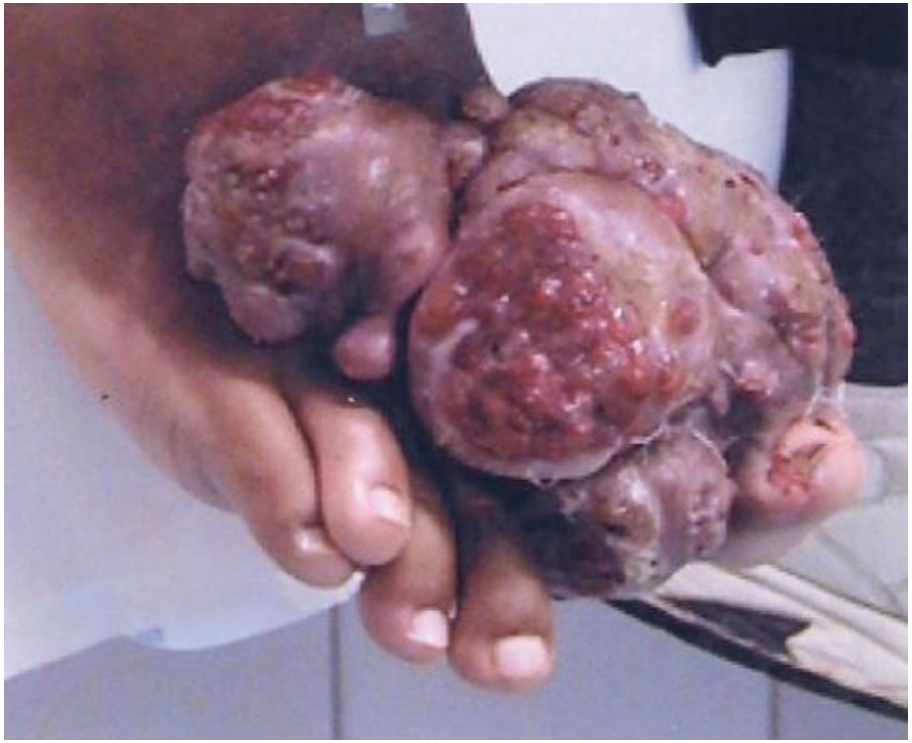
- The tumor develops as a result of the enlargement of existing nodules and formation of new nodules.
- Generally it is firm and round but may be soft and lobulated.
- Enlarged nodules open to the skin through sinus tracts, discharging sanguineous, seropurulent or purulent exudate that contains grains (Figs. 1, 2, and 3).



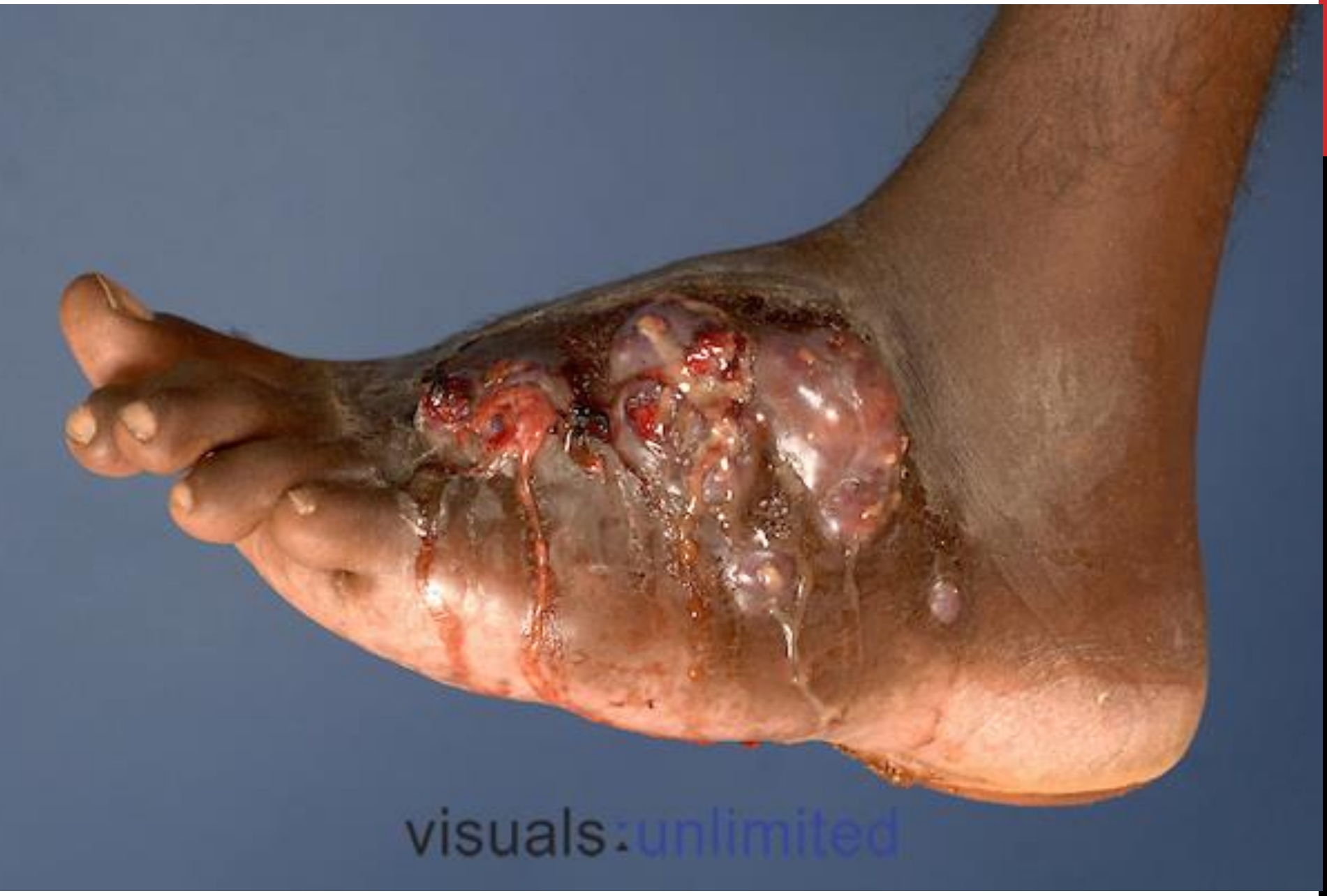
Eumycetoma on the plantar surface of the foot showing tumor and fistulae



Eumycetoma due to Madurella mycetomatis showing multiple sinus tracts



Large tumor from eumycetoma due to Madurella mycetomatis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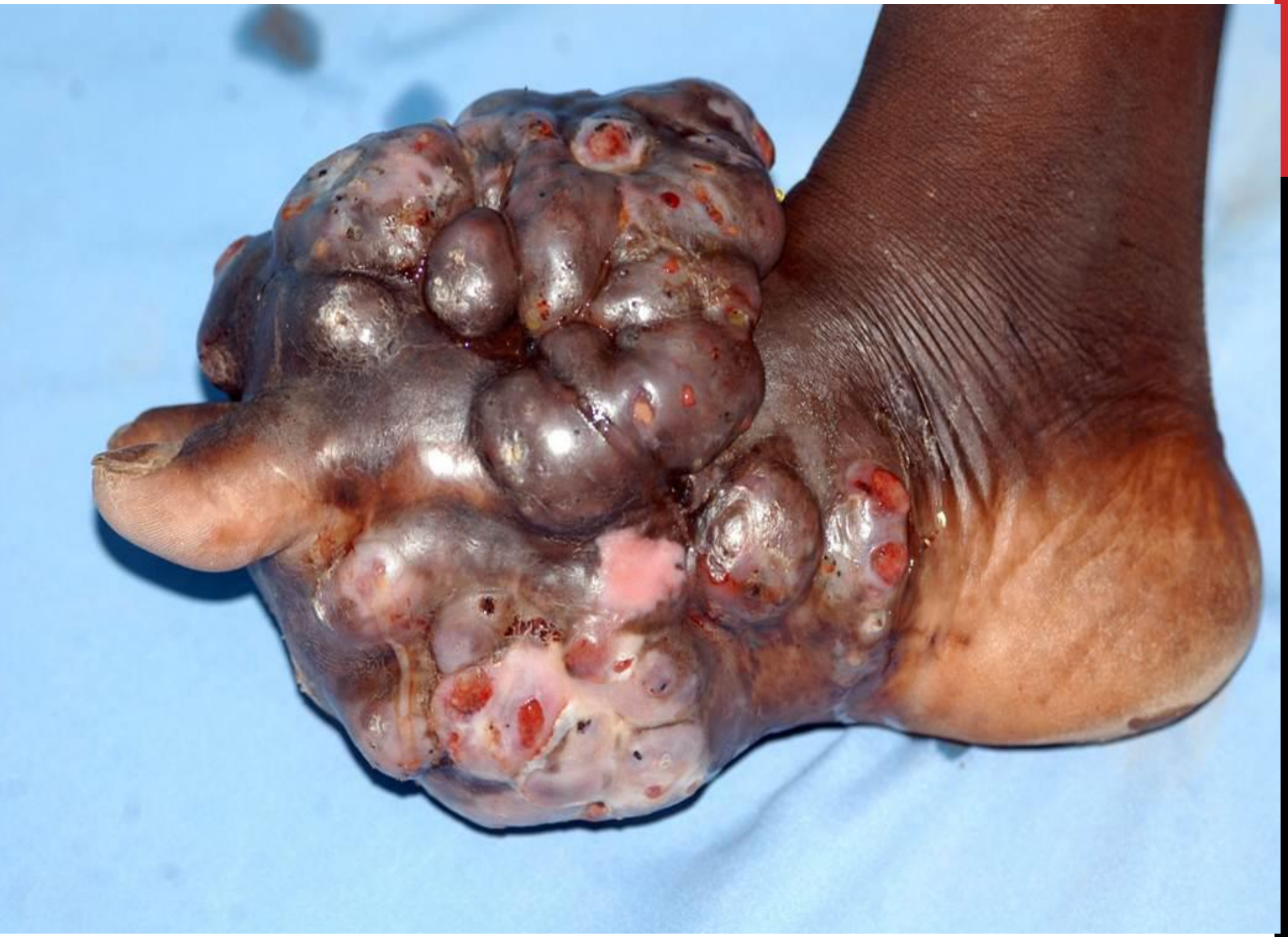

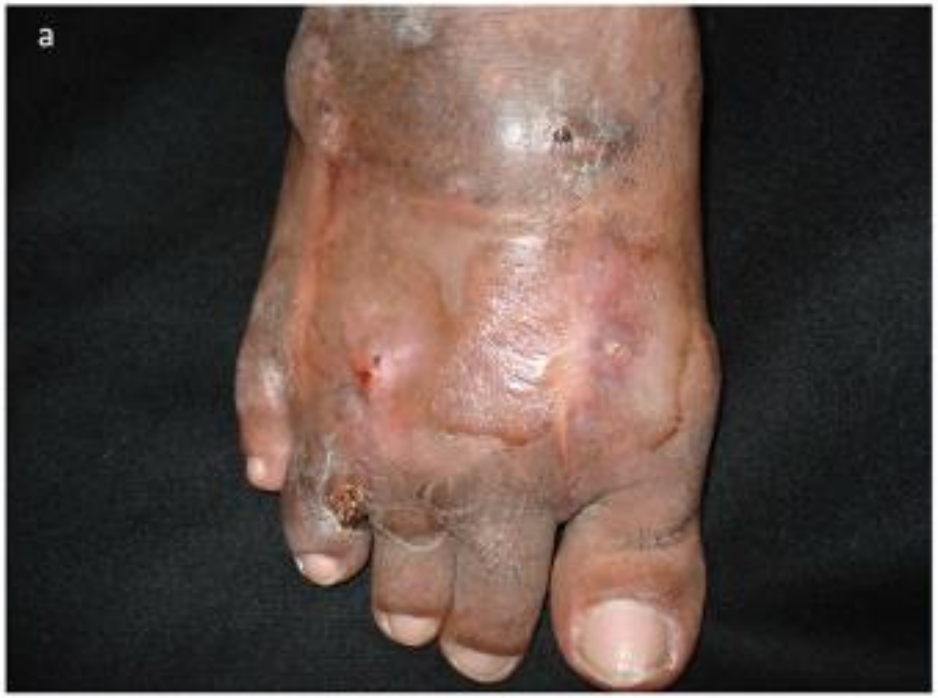
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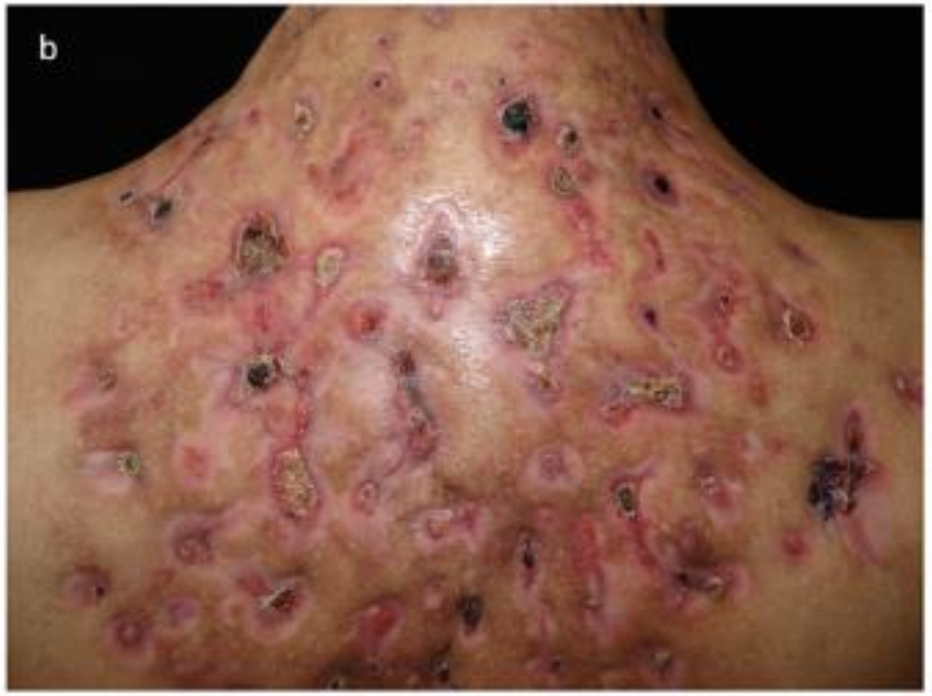
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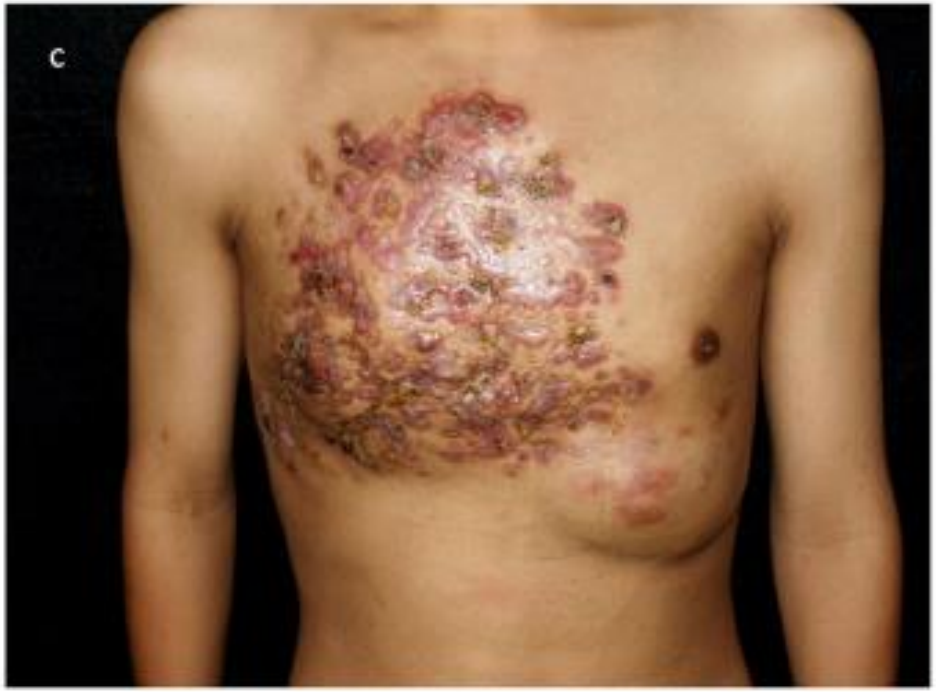
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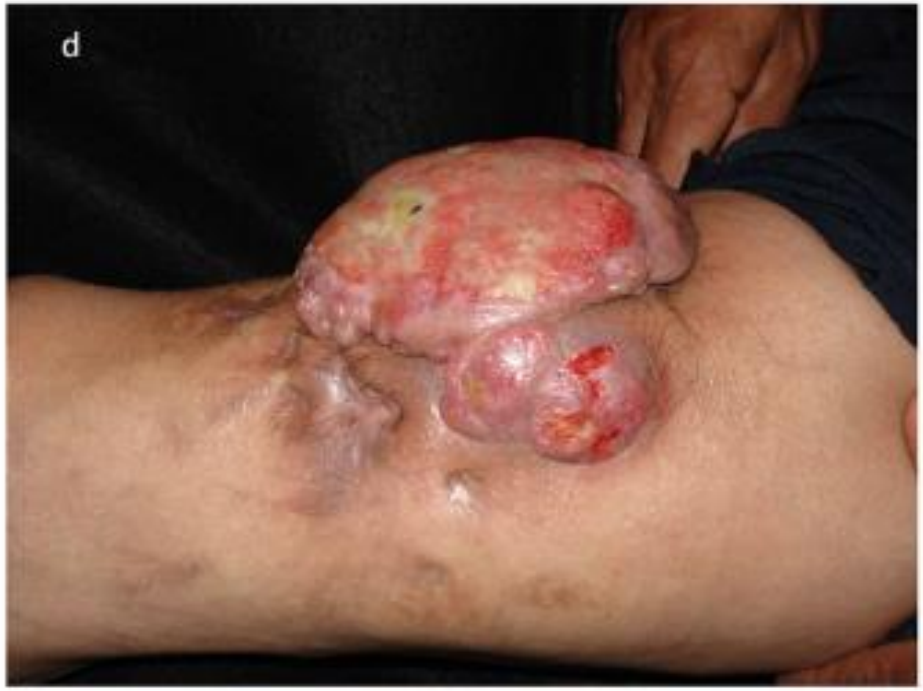
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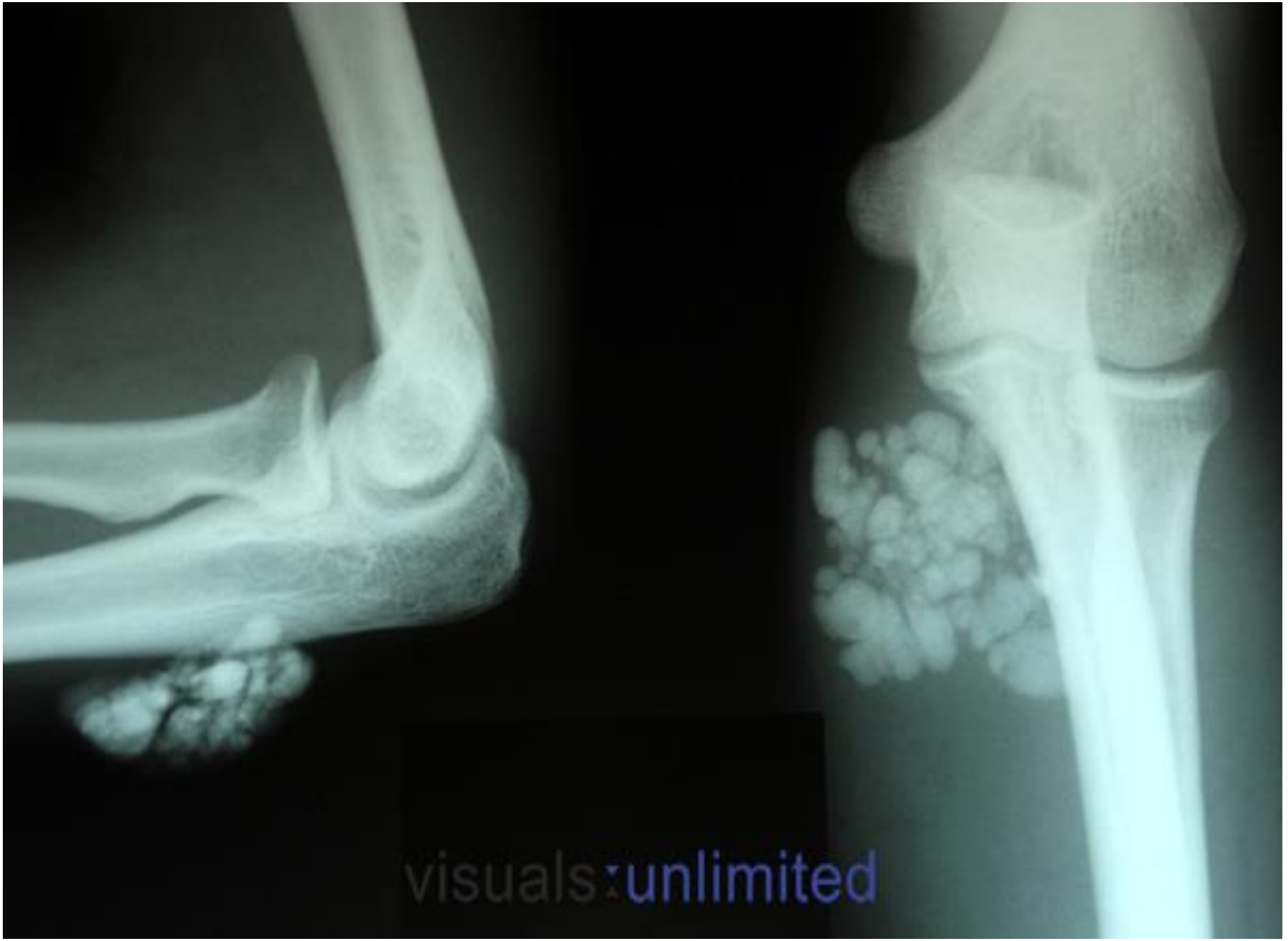
- Sinus tracts develop relatively early in the course of disease; at least one-third of patients develop sinuses between 3 and 6 months, and almost all patients have sinus tracts within 1 year of the development of skin lesions.
- Established sinuses heal and recur as new sinuses continue to develop.
- Destruction of adjacent structures can be dramatic and is especially characteristic late in the course of the disease.

- Destructive lesions are relatively painless. Pain, fever, and other systemic symptoms are not characteristic of eumycetoma, and when present, suggest a secondary bacterial infection.
- Bacterial cellulitis should be ruled out when pain is present, especially when edema and increasing discharge are evident.
- Massive fibrosis occurs after healing of involved tissue, contributing to the tumor-like appearance and woody texture of the affected area.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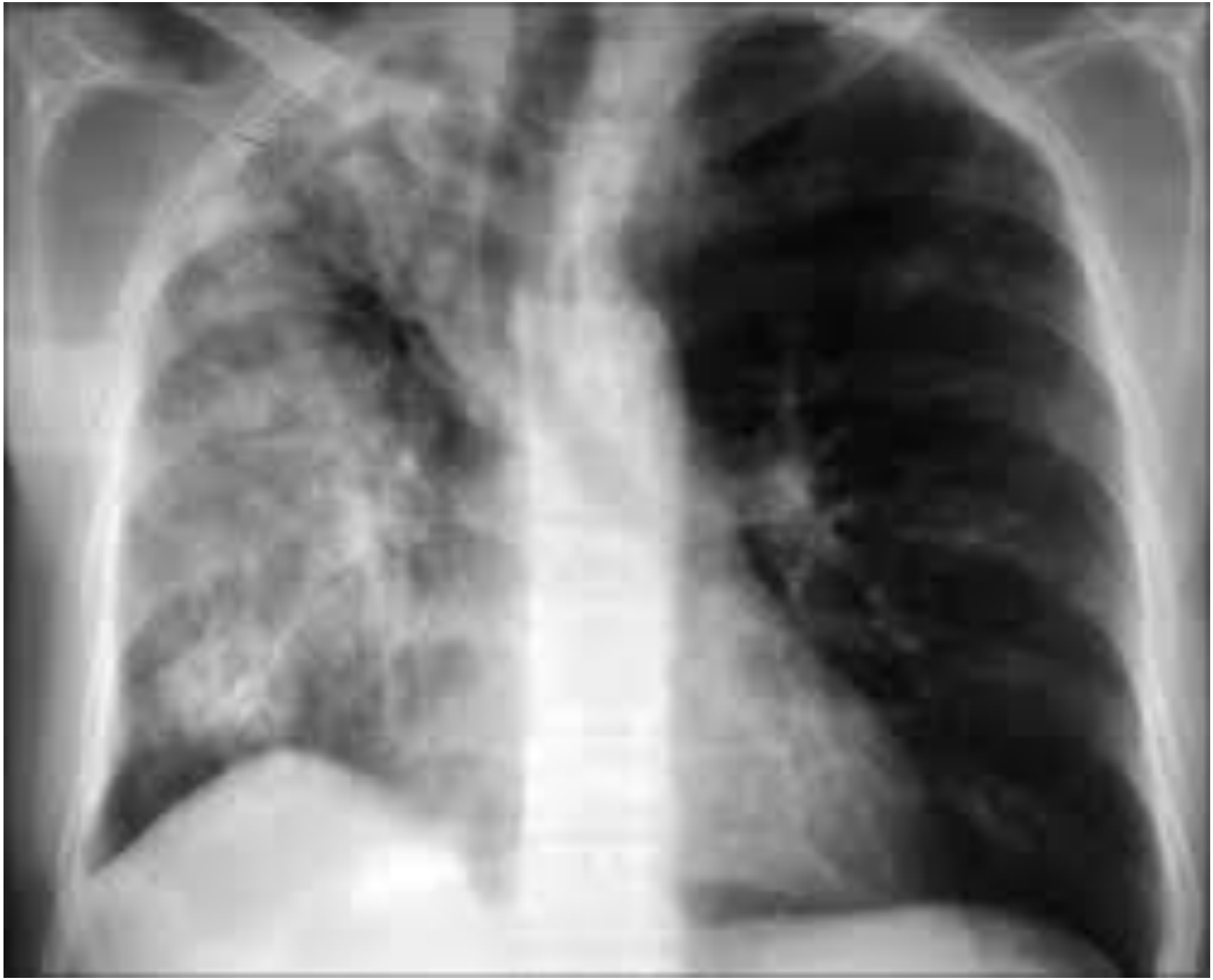

- Eumycetoma lesions are located most frequently in areas with a high frequency of repeated trauma, especially the lower limbs.
- Feet, legs, and hands account for approximately 90% of black grain eumycetomas and 95% of M. mycetomatis eumycetomas.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of eumycetoma lesions at any stage of their evolution should always include actinomycetoma due to aerobic filamentous actinomycetes and botryomycosis, due to gram-positive and gram-negative bacteria.
- Small eumycetoma lesions may be confused with folliculitis, soft tissue tumors. or cystic lesions , while exophytic verrucous eumycetoma lesions of the foot can mimic verrucous tuberculosis, blastomycosis, chromoblastomycosis, and sporotrichosis.

- More extensive tumoral pedal lesions without sinus tracts should be differentiated from elephantiasis of the foot, as well as benign and malignant tumors.
- When bone involvement is present, the differential diagnosis includes bacterial osteomyelitis, osseous tuberculosis, osteosarcoma, and other malignant bone tumors.

DIAGNOSIS

Evaluation of Grains

- Grain color, size, shape, and consistency should be noted because these characteristics help to guide identification of the causative fungus.
- For example, *M. mycetomatis* grains are large, black, and hard; *L. senegalensis* grains are large, black, and firm to hard; *M. grisea* and *P. romeroi* grains are small, black, and soft to firm; and *P. boydii* complex and *Aspergillus nidulans* grains are large, white, and soft.
- After macroscopic examination, grains should be placed in a drop of 10–20% KOH on a slide, compressed between two slides, and examined under microscopy.
- This direct examination will differentiate the grains of eumycetomas from the grains of actinomycetomas.
- Eumycetoma grains contain intertwined, broad hyphae (2–5 mm), and may contain large swollen cells (15 mm or more) at the periphery.

Culture

- Culture is essential for an etiologic diagnosis; however, performing cultures with eumycetoma specimens is laborious and complicated by a high rate of bacterial contamination.
- Prior to culture, grains should be washed several times with sterile saline solution to reduce bacterial and mould contamination, then crushed using sterile technique and plated on Sabouraud's dextrose agar containing chloramphenicol.
- 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 at 37°C for 6–8 weeks.
- Species identification is based on both macroscopic and microscopic examination of colonies.

TREATMENT
ANTIFUNGAL AGENTS

- Liposomal amphotericin B has been used to treat eumycetomas caused by *M. grisea* and *Fusarium* species,
- Black grain eumycetoma agents are sensitive in vitro to the older azoles, with itraconazole demonstrating the most activity, followed by ketoconazole and miconazole.
- Among the new triazoles, posaconazole is highly active in vitro against Aspergillus species and *P. boydii* complex, and voriconazole is active in vitro against *M. mycetomatis*, *M. grisea*, and E. jeanselmei.
- Voriconazole also has in vitro fungicidal activity against Aspergillus species and is more active than itraconazole against *P. boydii* complex isolates.
- In general, itraconazole and ketoconazole appear to perform better against black grain than white grain eumycetomas.
- Fluconazole 400 mg per day is not effective for eumycetoma caused by *M. mycetomatis, M. grisea,* or *P. boydii* complex.