

Subcutaneous mycoses

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Subcutaneous mycoses

Introduction

The term subcutaneous mycosis means a disease in which the pathogen, an exosaprophyte, penetrates the dermis or even deeper during or after a skin trauma. The lesions gradually spread locally without dissemination to deep organs. However, most fungi which cause subcutaneous mycoses can also occasion deep mycoses in patients with severe underlying abnormalities (via the respiratory tract).

Mycologically the pathogens of subcutaneous mycoses have only a few common characteristics and belong to very different taxonomic groups.

Subcutaneous mycoses occur exclusively or predominantly in the tropics. This is related on the one hand to the geographical distribution of the pathogens and the ecological factors that determine their saprophytic growth and sporulation and on the other hand it is also the consequence of the medical underdevelopment in these regions. Imported or indigenous cases are only rarely found in Western Europe.

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Chromomycosis

Clinical presentation

This chronic dermal/epidermal mycosis, also known as chromoblastomycosis is characterised by vegetative and verrucous lesions, which occur predominantly on the lower limbs. In addition erythematous, nodular or ulcerating lesions are sometimes also found.

Pathogens

The pathogens are dark-walled fungi (*Fonsecaea pedrosoi*, *Fonsecaea compacta*, *Cladosporium carionii*, *Phialophora verrucosa* etc.), which are saprophytes on plants and wood.



Chromoblastomycosis. Copyright ITM



Chromoblastomycosis, syn. chromomycosis; hyperkeratotic lesions foot; Fonsaceae (*Phialophora*) infection, copyright ITM

Diagnosis

Microscopic examination of crusts in KOH shows the presence of irregular, 10-20 μm large, brown-walled elements with transverse septa, 'sclerotic cells'. The specific causative agent can only be identified by culture.

Treatment

1. Many clinicians find chromomycosis very resistant to antifungal treatment.
2. Surgery if possible (ideal for incipient lesions)
3. Heat therapy, as well as cryotherapy (for lesions with limited extend)

4. Itraconazole : 200-400 mg/day (+ 5-fluorocytosine: 100-150 mg/kg/day)
5. Saperconazole might be more effective than itraconazole
6. Terbinafine : 500 mg/day for 6-12 months, after 2-4 months a reduction of 70% of the sclerotic cells is seen, Cure: 40% after 4 months, 75% after 8 months, 83% after 12 months. Terbinafine might be the first choice treatment.
7. Japan: fluconazole 200 mg/day + heat therapy (improvement after 2 weeks!)
8. Some patients have responded favorable to treatment with amphotericin B
9. Dematiaceous fungi are very sensitive (in vitro) to the new triazoles voriconazole and posaconazole, but further clinical data are needed.
10. The place of the latest triazoles isavuconazole, ravuconazole and albaconazole is still unclear but if a parallel with their action against other fungal infections can be made, they might be promising.

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Mycetoma

Mycetomas are chronic, inflammatory swellings with numerous sinuses, caused by moulds or bacteria. The causative agent can be seen in the bloody or non-bloody pus and sometimes with the naked eye in the form of granules. In 75% of cases, a mycetoma is localised on the foot (Madura foot). In addition to involvement of soft tissue; bone tissue is severely affected with osteolysis on the one hand and hyperostosis on the other.



Madura foot patient in King Saud Medical Complex. Riyadh. Saudia arabia
(Image source: Haitham Alfalah, Halfalah)



Mycetoma of shoulder and back

Pathogens

Mycetomas are caused by 2 totally different groups of organisms: the first are moulds and the second are filamentous bacteria in the order Actinomycetales. In the first case they are referred to as eumycetomas (mainly Africa), in the second as actinomycetomas (mainly Latin-America). Also in India, mycetoma is prevalent. The difference is very important for therapy. All causative agents of fungal mycetoma are exosaprophytes that have penetrated deep into the tissue with a splinter of wood or a thorn. The primary reservoir of the causative agents is believed to be the soil. The limited geographical distribution of most pathogens and their natural history explain why mycetomas occur practically exclusively in the tropics. Eumycetoma can be caused by more than 42 different fungal species.

Diagnosis

The differential diagnosis between fungal and actinomycotic mycetomas is based on the examination of the granules and/or culture. The compact microcolonies of the causative agents differ from one another in terms of colour, shape, dimensions and composition. Black granules are always of fungal origin (e.g. *Madurella mycetomatis*); small red granules are specific for the actinomycotic *Streptomyces pelletieri*; whitish-yellow granules can be fungal or actinomycotic in nature.

In the direct examination of a crushed granule in KOH, the distinction between fungal and actinomycotic granules can be made on the basis of the presence or absence of true hyphal fragments.

Most information is obtained from the histological examination of a deep biopsy taken from around the path of a sinus. Vesicular or filamentous elements are seen in fungal granules (Gomori-Grocott stain). Only *Madurella mycetomatis* the most common causative agent of eumycetoma, can be detected histologically by the presence of a brown cement. With the other moulds identification should be made by culture.

New DNA-isolation techniques on fungal cultures (takes 6 weeks) or directly on the grains (immediate result) are under development. Serological tests exist but don't detect all different species and are not used in routine diagnosis.

Treatment

Until recently only surgical removal of the whole affected area was successful in treating eumycetoma.

Itraconazole for 12 months (or longer) in combination with removal of the mass, is the current the treatment of fungal mycetomas, but only results in 37% cure rate. The newer azole derivatives posaconazole, voriconazole, isavuconazole and ravuconazole have excellent in-vitro activity. Their real life efficacy is under review and isolated case studies have shown resolution of symptoms with these agents. For actinomycetoma, the first choice treatment is combination treatment of 2 drugs, such as streptomycin or amikacin IV with dapsone or cotrimoxazole for a long duration (depending mainly of the causative pathogen). New data suggest that co-amoxiclav (Augmentin™) acid can be used instead of aminoglycosides to reduce ototoxicity and kidney toxicity.

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Sporotrichosis

Etiology

Sporotrichosis is only caused by the mould, *Sporothrix schenckii*. It is an exosaprophyte on plants, wood and in the soil (peat moss). *S. schenckii* is a dimorphic mould. At 37°C and on rich nutrient media the yeast phase is obtained with oblong yeast cells.

Clinical aspects



Sporotrichosis lesions with spread via the lymphatics. Copyright Alexander von Humboldt Institute, Peru

The classic presentation is the lymphocutaneous form. After an initial lesion, the inoculation chancre, subcutaneous nodules appear followed by ascending lymphangitis. The nodules progressively penetrate the skin and ulcerate. The most common localisations are the hand and the forearm. In addition to this typical lymphocutaneous form there is also one with disseminated skin lesions, a local cutaneous form, often on the face which according to some authors occurs in re-infections and extracutaneous sporotrichosis with involvement of the mucous membranes, bone, muscles, lungs or systemic infection. Pulmonary localisations without involvement of other organs occur in endemic areas (South America) probably more than is thought. This chronic pulmonary disease is often mistaken for smear-negative tuberculosis or chronic pulmonary aspergillosis.

Differential diagnosis:

1. *Sporothrix schenckii*
2. *Blastomyces dermatitidis*
3. *Coccidioides immitis*
4. *Cryptococcus neoformans*
5. *Histoplasma capsulatum*
6. *Mycobacterium marinum*, *M. chelonae*, *M. abscessus*, *M. kansasii*
7. *Nocardia brasiliensis* and *N. asteroides*
8. *Leishmania* sp (mainly *L. guyanensis*).
9. *Francisella tularensis*
10. *Staphylococcus aureus*
11. *Streptococcus pyogenes*
12. *Bacillus anthracis*
13. *Burkholderia pseudomallei* (melioidosis)

Diagnosis

In contrast to all other mycoses, the diagnosis of sporotrichosis is based not on the detection of the pathogen by direct or histological examination, but solely on culture. It involves collecting a small quantity of the milky pus from ulcerated lesions after the removal of the superficial crusts and then inoculating it onto a Sabouraud nutrient medium. Growth is obtained after a few days of incubation at 25°C and the typical asexual spore formation is easily identified.

Treatment

For cutaneous forms, oral potassium iodide (saturated solution 1g/ml) can be used. As an alternative, terbinafine 2 x 250 mg/day for maximum 32 weeks can be used. Cure can be expected after 8 weeks. Local heat therapy (I.R. or compresses) is sometimes used. The killing rate of the fungal cells is markedly higher at 40°C than at 37°C. Itraconazole and terbinafine can be used of for small lesions, as well as for systemic cases. Amphotericin B (liposomal formulation is preferred) is preferred for severe cases. Posaconazole (Noxafil) has good in vitro activity against *S. schenkii*, but more clinical data are needed. Fluconazole (Diflucan), voriconazole (Vfend) and ravuconazole are ineffective in sporotrichosis.

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Rhino-entomophthoromycosis



Rhinoentomophthoromycosis; nasofacial phycomycosis; *Coniodobolus coronatus* (Entomophthora coronata), copyright ITM



Rhinoentomophthoromycosis; nasofacial phycomycosis; *Coniodobolus coronatus* (Entomophthora coronata), copyright ITM



Rhinoentomophthoromycosis; subcutaneous phycomycosis; *Conidiobolus coronatus* (Entomophthora coronata), copyright ITM

Zygomycosis is a term referring to infections with zygomycetes, and more specifically infections such as mucormycosis and entomophthoromycosis (synonyms of the latter are the tongue-twisting and jaw-breaking “rhino-entomophthoromycosis” and “rhino-entomophthoramycosis”). Rhino-entomophthoromycosis is a slowly progressing tropical infection of the subcutaneous tissue or paranasal sinuses caused by *Conidiobolus coronatus* or related species. Severe mutilations with grotesque deformation of the face can ensue. Basidiobolomycosis is often considered together with rhino-entomophthoromycosis. *Basidiobolus ranarum* affects subcutaneous tissue in areas such as buttocks, thighs and arms. Localisation in the face results in severe facial swelling, with gross deformity of eyelids and cheeks. The differential diagnosis includes Burkitt’s lymphoma. Lymphatic filariasis usually presents in a different manner.

Histopathology will show fungal elements, granulomata and eosinophils. Culture will confirm the diagnosis. Azoles such as itraconazole or the allylamines terbinafine – with or without surgery – should be tried as treatment, although there is insufficient clinical experience. Amphotericin B is an option for *Basidiobolus* infections.

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Lobomycosis

Lobomycosis is a very rare infection. It is a self-limited chronic fungal infection of the skin endemic in rural regions in South America and Central America. The prevalence of the disease is high among the Caiabi Indians of Brazil and among the Amoruas tribe of the Casanare state in Colombia. It was the Brazilian physician Jorge Lobo who in 1931 in Recife first described this infection. He gave the name keloidal blastomycosis. The condition was called Lobo disease in 1938, and in 1958 the name lobomycosis was applied.

The organism responsible for lobomycosis has yet to be cultured in vitro. The causative organism is a blastomycosis *Lacazia loboi*, formerly named *Loboa loboi*. The natural reservoir of the pathogen is unknown. Its likely habitat is somewhere in the rural environment because the disease occurs in humans living in rural areas. Soil and vegetation seem to be likely sources of infection. Since the pathogen has been recovered from lobomycotic lesions of *Tursiops truncatus* (“bottlenose dolphins”)

in Florida and in the Bay of Biscay in Europe, an aquatic reservoir seems likely. A case of dolphin-to-human transmission has been documented in 1983 in a dolphin handler. As for clinical symptoms the name keloidal blastomycosis describes the lesions very well. Lobomycosis often develops at sites of minor trauma but sometimes no history of trauma can be recalled. The disease predominately affects exposed areas and extremities. Skin lesions slowly develop over time. Only after the lesions have become large do patients tend to consult a doctor. The lesions often begin as small papules or pustules, mildly pruritic or resulting in a burning sensation. The disease leads to verrucous or lobulated keloidal nodules and crusty plaques. Lesions are well defined, smooth and painless. They are easily moved around since they lie free over the deeper tissues. Older lesions typically become wart-like and ulcerative with satellite lesions resulting from autoinoculation. The mucosae are spared. The disease does not seem to heal spontaneously. The infection may spread proximally from the extremities suggesting lymphatic dissemination. Patients lack other systemic symptoms and lobomycosis does not affect the general health of the patient although squamous cell carcinoma has been described on old scar lesions. Keloids are the most important differential diagnosis and are much more common.

Diagnosis relies on a skin biopsy. The fungus is abundant in lobomycotic skin lesions. It is a spherical intracellular yeast 6-12 μm in diameter. The melanin-containing birefringent 1 μm thick cell wall resists digestion by macrophages. Linear or radiating chains of 5-10, even 20 organisms linked by tubules are characteristic. The organism can be seen with haematoxylin and eosin but the best stain is Grocott silver-methenamine which will show the typical yeasts chains. Attempts at medical treatment have failed. Surgery is successful only when the lesion is small and can be fully resected. Repeated cryotherapy appears to be more successful. The present antifungals do not seem promising, but more study is needed. Cases of successful treatment with posaconazole have been described. Clofazimine and dapsone have been tried with limited success.