MYCETOMA
(worse than the thorn itself!!)
INTRODUCTION

• Mycetoma is a chronic progressive granulomatous exogenous infection of subcutaneous tissue characterized by swelling & presence of granules of the etiological agent which may spread contiguously to involve adjoining skin with formation of multiple sinuses discharging pus, granules, fragments of degenerated muscles, tendons & bones.
HISTORY

- “Padavalmika” (foot anthill): Atharva-veda
- Dr. John Gill, 1842: “Madura foot”
  - “when the leg has been amputated, the foot has been found to be one mass of disease of fibrocartilaginous nature, with entire destruction of joints, cartilages & ligaments; it has neither shape nor feature & is covered with large fungoid excrescences discharging an offensive ichorous fluid.”
- Vandyke Carter, 1860: “Mycetoma”
- Kanthack, 1892 & Vincent 1894
- Brumpt, 1905: genus *Madurella* and described multiple fungal etiologies
- Pinoy, 1913: divided into “actinomycosis” & “true mycetoma”
• Chalmers, Archibald & Christopherson (1913-16):
  • “maduramycosis” (true mycetoma)
  • Included all body sites
• Currently:
  • Actinomycotic mycetoma
  • Eumycetoma
EPIDEMIOLOGY & ECOLOGY

- Tropics & sub tropics, but sporadic in temperate zones
- Latitude 15° S and 30° N: “Mycetoma belt”
- Arid regions, short rainy season, little temperature fluctuations
- Extremely rare to have infection by more than one species in the same individual
- Endemic countries
  - India, Sudan (*M. mycetomatis*)
  - Mexico (*N. braziliensis*) & Senegal
  - Somalia, Egypt, Uganda, Nigeria, Chad, Algeria, Mauritania, Mexico, Venezuela
  - USA, Japan, S. Arabia, Rumania
- *M. mycetomatis*(19%) & *Nocardia* spp.(32%)
MYCETOMA BELT
Eumycetoma
• Nigeria: *S. somaliensis*
• S. Arabia: *S. somaliensis*
• Mexico: *N. brasiliensis* (86.6%), *A. madurae* (10.2%)
• Brazil: actinomycetes (68%), commonest *N. brasiliensis*
  • True fungi 32% cases
    • *M. mycetomatis*
    • *M. grisea*
    • *Scedosporium apiospermum*
India

- Vanbreuseghen stated that mycetoma occurs in
  - Rainfall: 50-500 mm/yr
  - Temperature: 15-25°C
- But, in India conditions vary amongst different geographic locations
  - Actinomycotic: S. India, N. India
  - Eumycetoma: NW India
- Maximum cases
  - Rajasthan
  - Tamil Nadu
Rajasthan

- 3 arbitrary regions (rainfall, soil)
  - NW desert region (rainfall < 350mm/yr)
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  • SE Aravali hill region (rainfall > 600 mm/yr)
    • Eumycetoma:actinomycetoma; 1:2
• Singhvi et al, 1995 (Jodhpur, Rajasthan): higher prevalence of actinomycetoma from extra pedal sites
• Overall, Actinomycetoma > Eumycetoma
• Tamil Nadu, Actinomycetoma = Eumycetoma
• Rajasthan,
  • *M. mycetomatis* > *S. somaliensis, A. madurae, Nocardia* spp.
  • Least common, *M. grisea, Leptosphaeria senegalensis, Phialophora* spp., *P. boydii, A. pelletieri*
  • *Nocardia* spp. was more common in SE Rajasthan
- South India
  - *M. mycetomatis*
  - *A. madurae*
  - *A. pelletieri*
  - *Nocardia* spp.
  - *Leptosphaeria senegalensis*
  - *Leptosphaeria tompkinsii*
  - *Pseudoallescheria boydii*
  - *Acremonium kiliense*
  - *Acremonium falciforme*

From soil samples:
- *M. mycetomatis*
- *P. boydii*
- *S. somaliensis*
- *N. asteroides*
- *N. braziliensis*
- *N. caviae*
• Prevalent throughout India
  • Tamil Nadu, Pondicherry, A.P.
  • Rajasthan, Gujarat, Maharashtra
  • Punjab, Delhi, Haryana, Chandigarh
  • Bengal
• *Nocardia* spp. infections more common in SE India
  • *N. brasiliensis*
  • *N. asteroides*
  • *N. caviae*
  • *N. transvalensis*
Chandigarh

- Infrequent
- 1967-1977: 20 cases
- 1980-96: 23 cases
  - Actinomycotic agents: 56.5%
  - Eumycotic agents: 43.5%
  - *Madurella mycetomatis*, most frequently isolated
  - Other agents isolated were *N. asteroides*, *A. madurae*, and *Streptomyces* spp. and *M. grisea* was least common
  - Foot was the commonest site of infection
  - Males and females were found to be equally affected
• Vegetations: acacia tree
• *S. somaliensis* in hot & dry climates, with rainfall <250mm/yr, whereas *Pyrenochaeta romeroi* in areas with higher rainfall
• Male:female ratio; 4:1
  • Mendez-Tovar et al have shown that progesterone can inhibit the growth of *M. mycetomatis* and *Pyrenochaeta romeroi*, which might contribute to the sex bias in the incidence of mycetoma
• Rural workers 16-45 yrs old, rarely in non-manual workers
  • Occupation predisposes to trauma
EUMYCOTIC MYCETOMA AGENTS

White granules

- *Acremonium falciforme* (soft,<1)
- *Acremonium kiliense* (soft, irregular, >1.5)
- *Acremonium recifei* (soft,<1.5)
- *Cylindrocarpon cyanescens*
- *Cylindrocarpon destructans* (oval, 0.5)
- *Pseudallescheria boydii* (lobulated, oval, >1)
- *Fusarium oxysporum*
- *Fusarium moniliforme* (soft,<1)
- *Fusarium solani* (oval, <1.5)
- *Aspergillus nidulans* (soft, ovoid, <0.6)
- *Polycytella hominis* (soft, 0.5-1)
- *Neotestudina rosatii* (soft, <1)
Black granules

- *Curvularia geniculata* (irregular)
- *Curvularia lunata* (ovo-lobular,<1)
- *Leptosphaeria senegalensis* (tubular,hollow,<1.2)
- *Leptosphaeria tompkinsii* (irregular,1)
- *Madurella grisea* (soft,oval to lobulated,<1)
- *Pseudochaetosphaeronema larense*

Green granules

- *Aspergillus flavus*
- *Pyrenochaeta mackinnonii* (firm,ovolobular,0.5-1)
- *Pyrenochaeta romeroi* (soft,oval to lobulated,<1)
- *Madurella mycetomatis* (hard,brittle,oval to lobulated,<2)
- *Exophiala jeanselmei* (soft,0.2-0.3)
- *Phialophora verrucosa*
- *Plenodomus avramii*
- *Corynespora cassiicola*
ACTINOMYCOTIC MYCETOMA

- *Nocardia asteroides* (soft, irregular, 1)
- *Nocardia brasiliensis* (lobular, soft, 0.5-1) - White
- *Nocardia transvalensis* (lobed, 2)
- *Nocardia caviae* (soft, lobular, <1) - White to yellow
- *Nocardia dassonvillei* (<0.5) - Cream
- *Actinomadura madurae* (soft, oval, 1) - White to yellow or pink
- *Streptomyces somaliensis* (hard, spherical, 0.5-2) - Yellow to brown
- *Actinomadura pellitieri* (hard, oval, 0.3-0.5) - Red
**SOURCE & MODE OF INFECTION**

- Exogenous
- Thorn pricks
- Minor abrasions & trauma to skin
- Perineal mycetoma:
  - Due to inadequate clothes over groin & working in squatting position in the fields
  - Cleaning of perianal region with soil after defecation
- Use of straw wicks for cleaning the external ear
- Carrying bags/ wood on the back/ shoulders/ head
- H/O guinea worm extraction by using thorns
- Domestic fencing using thorny shrubs or tree branches
• Recovery rate of fungi from soil: 25% & from thorns: 16%  
  (Singhvi et al, 1995)

• Occupational hazard to farmers, herdsman, field workers  
• Walk barefooted  
• Also to carpenters, builders and land workers
MYCETOMA SITES

- Foot – 80%, left>right
- Hand, right>left
- Knee, arm, leg, head and neck, thigh, perineum
- Rarely, chest, abdominal wall, mandible, paranasal sinuses, eyelid, vulva, orbit, scrotum, surgical incisions
MYCETOMA SPREAD

- May spread along the fascial planes involving – skin, subcutaneous tissue & underlying structures
- Spares nerves and tendons
- Spread is rapid and extensive in case of involvement of trunk and buttocks
- Bone involvement early in mycetoma of scalp
• 1-3% lymphatic spread to the regional lymph nodes – may suppurate & discharge
  • More common with actinomycetoma
  • Incidence augmented – repeated incomplete surgical excision attempts
• Blood borne spread – reported only in case of infection by Nocardia and Streptomyces
CLINICAL PRESENTATION

- Clinical presentation in both the conditions is almost similar
- Presents as slowly progressive, painless, subcutaneous swelling, usually firm & rounded but may be soft, lobulated, rarely cystic & mobile on palpation
- Multiple secondary nodules – may suppurate – multiple sinus tracts
- Sinus tracts keep healing & developing at the same time
- Discharge – serous/ serosanguinous/ purulent
- Grains discharged during the active phase
- Usually painless (?)anaesthetic substances, ? Nerve damage
- Skin changes
- Local hyper-hydrosis
CLINICAL PRESENTATION

- Triad of Symptoms
- Tumefaction i.e tumor like swelling
- Multiple draining sinuses
- Presence of granules
• Actinomycetoma
  • Rapidly progressive
  • Lesion is more inflammatory, destructive & invades the bone early
• Eumycetoma
  • Slowly progressive
  • Clear defined margins of the lesion
  • Remain well encapsulated for a long time
Botryomycosis: “a close mimic”

- A rare, chronic, persistent bacterial infection also characterized by formation of draining sinuses & grains
- Clinically & histologically resembles actinomycosis
- May metastasize
- Skin, head, pinna, hands, feet
- Etiology
  - *S. aureus, S. epidermidis*
  - *E. coli*
  - *P. aeruginosa*
  - *Proteus spp.*
  - Non hemolytic *streptococci*
  - *Bacteroides spp.*
  - *Rhodococcus spp.*
• Two types:
  • Cutaneous: simple inflammatory nodules to discharging
    sinuses and ulcers/ fistulae
  • Usually localised
  • more on hands, feet and head

• Visceral type: in chronically ill
  • Lungs mostly involved

• Treatment depends on organism sensitivity
PATHOLOGY of Mycetoma

• In tissues, \textit{M. mycetomatis} forms numerous black sclerotia (grains)
  • Grains are vegetative aggregates of the fungal mycelia embedded in a hard brown matrix

• This matrix consists of extra-cellular cement (1,8-dihydroxynaphthalene melanin) in combination with host tissue debris
  • Rigid matrix might act as a barrier protecting the fungus from the natural immunity of the host and antifungal agents
  • Melanins are thought to be protective in circumstances of host-induced oxidative stress
• Grains
  • Different shapes and sizes
    • Mostly rounded, oval, or lobulated
  • Two types of grains have been identified
    • Filamentous
      • Consists of brown, septate and branched hyphae that might be slightly more swollen and thick towards the periphery of the colony
    • Vesicular
      • Less common, has a cement-like matrix in the cortex and a central area filled with numerous vesicles (6–14 μm in diameter) and light-coloured hyphae
**Histological differences**

<table>
<thead>
<tr>
<th>ACTINOMYCETOMA</th>
<th>EUMYCETOMA</th>
</tr>
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<tbody>
<tr>
<td>Late stages: acute suppurative pyogenic reaction persists</td>
<td>Foreign body granuloma with epithelioid hyperplasia &amp; giant cell formation</td>
</tr>
<tr>
<td>More extensive &amp; obliterate involvement of bone with lytic &amp; hypertrophic changes</td>
<td>Late bone involvement with lytic but no hypertrophic involvement</td>
</tr>
<tr>
<td>Invades muscle more readily</td>
<td>Not so</td>
</tr>
<tr>
<td>Produce cellular proliferation around the sinus opening-raised border</td>
<td>No cellular proliferation around the sinus opening</td>
</tr>
</tbody>
</table>
**DIAGNOSIS**

**Radiology**

- Calcification & obliteration of fascial planes
- Cortex may be compressed from outside – bone scalloping & periosteal reaction
- “Sun-ray appearance” & “codman triangle”
- Multiple bony cavities may be seen
  - Despite this pathological fractures are rare (? Filled with solid mass of grains & fibrous tissue)
- Skull: purely sclerotic, with loss of trabeculations
- Useful for follow up
Ultrasonography

- Can differentiate between eumycetoma/ actinomycetoma/ non-mycetomatous lesions

- Grain cement substance gives sharp bright hyper-reflective echoes

- Ultrasonographic diagnosis is more precise & accurate when no discharging sinuses are there: planning surgical excision
MICROBIOLOGICAL DIAGNOSIS

• Specimens
  • Pus
  • Exudate
  • FNAC
  • Excised tissue/Biopsy
  • Grains from soiled bandage
• Lesions are cleaned with antiseptics
• Press the sinus from periphery to express exudate
• Granules collected on a sterile gauze

• Alternatively, collected with the help of a loop

• If more granules needed, lift the flap of the lesion with the help of a loop and collect granules in a petri dish
**Direct examination**

- Granules are first washed in normal saline a number of times
- Size, shape, colour, consistency of granules
- 10% NaOH mount
  - Size of hyphae
  - Septation
  - Pigment formation in hyphal walls
Morphology

EUMYCOTIC GRAINS
- 2-6 µm wide hyphae, often have large, globose swollen cells (upto 15µm) at margins

ACTINOMYCOTIC GRAINS
- Filaments with diameter of 0.5 – 1 µm, as well as coccoid to bacillary elements
- Usually gram positive filaments
• **GRAM STAIN PREPARATION**
  - Crush the grain between two slides, heat fix & stain
• **KINYOUN’S MODIFIED ACID FAST STAINING (1%)**
• **LPCB PREPARATION**
• **HISTOLOPMENTHOLYOGY**
  - GMS
  - PAS
  - H & E
**Culture**

- Grains washed in N/Saline & crushed before inoculation
- SDA with antibiotics
  - Media should not contain cycloheximide
- For actinomycetes
  - SDA with 0.5% yeast extract but without antibiotics
  - BHI
  - LJ media
  - Blood agar
- Incubation at 25 & 37° C
Serodiagnosis

- Immunodiffusion
- CIE
  - Not very useful
  - Suffer from poor specificity & sensitivity due to cross reactivity

PCR
- Targeting ribosomal gene complex
- Have been detected from biopsy as well as soil samples
TREATMENT

Eumycetoma

- Surgery is most acceptable
- Reports of successful chemotherapy: few
  - Ketoconazole
  - Itraconazole
- Prolonged chemotherapy (upto many years)
- Chemotherapy before & after surgery
Actinomycetoma

- Amenable to medical treatment
  - Streptomycin + dapsone
  - If no response: replace dapsone with cotrimoxazole  
    **FIRST LINE**
  - Amikacin with/ without cotrimoxazole (Welsh regimen)
  - Rifampicin
  - Sufadoxine + pyrimethamine  
    **SECOND LINE**
  - Sulphonamides
- Mean duration: 1 year
- Cure rate: 60-90%
EXPERIMENTAL MODELS

• Balb/c mice
  • *M. mycetomatis* mycelia in sterilized soil (adjuvant) given subcutaneously & intra-abdominal
  • Infection was inoculum dependant
    • ? Immune system may not be the culprit
### Eumycetoma vs. Actinomycetoma

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<th>Eumycetoma</th>
<th>Actinomycetoma</th>
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<tr>
<td><strong>Causative agents</strong></td>
<td>Fungi</td>
<td>Bacteria</td>
</tr>
<tr>
<td><strong>Lesion characteristics</strong></td>
<td>Well-encapsulated with a clear margin</td>
<td>Diffuse with no clear margin</td>
</tr>
<tr>
<td><strong>Sinuses</strong></td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td><strong>Colour of grains</strong></td>
<td>Different colours, but mostly white or black</td>
<td>Different colours, but not black</td>
</tr>
<tr>
<td><strong>Course of infection</strong></td>
<td>Slowly progressive</td>
<td>Inflammatory and rapid progression</td>
</tr>
<tr>
<td><strong>Bone invasion</strong></td>
<td>After a long time</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Cavities in radiograph</strong></td>
<td>Small in number, but large in size with clear margins</td>
<td>Numerous, small in size (except in case of Actinomadura madurae) with unclear margins</td>
</tr>
<tr>
<td><strong>Drug of choice</strong></td>
<td>Ketoconazole, Itraconazole</td>
<td>Dapsone+streptomycin Rifampicin or sulfadoxine pyrimethamine Amikacin+co-trimoxazole</td>
</tr>
<tr>
<td><strong>Medical treatment only</strong></td>
<td>Partial cure or improvement</td>
<td>Useful in most cases</td>
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…… could dramatically reduce the incidence!!