Review
Mycetoma

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Introduction

Mycetoma is a chronic specific, granulomatous, progressive, destructive inflammatory disease. It usually involves the subcutaneous tissue most probably after traumatic inoculation of the causative organism. Mycetoma may be caused by true fungi or by higher bacteria and hence it is classified as eumycetoma and actinomycetoma respectively.[1,2,3] A large variety of microorganisms from various genera and species are capable of producing mycetoma.[1,4]

The triad of painless subcutaneous mass, multiple sinuses and sero-purulent discharge containing grains is pathognomic of mycetoma. It may spread to involve the skin and the deep structures resulting in destruction, deformity and loss of function. Mycetoma commonly produces various disabilities and deformities & in many cases is difficult to treat and can be fatal. [3,5]

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Epidemiology

Mycetoma has a world-wide distribution but this is extremely uneven. It is endemic in many tropical and subtropical regions. It prevails in the mycetoma belt that stretches in a band between the latitudes of 15^0 South and 30^0 North. The belt includes Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia, Argentina and others. The mycetoma belt encases an area of forest trees and savannah, the dominant plants being various species of Acacia in addition to a variety of other thorny trees.

The geographical distribution of mycetoma and its individual causative organisms shows considerable geographical variations, which can be convincingly explained on an environmental basis.[6,7,8]

Route of Infection

The route of infection in mycetoma is unclear. The popular theory is that, the organisms are usually present in the soil in different forms. They are implanted into the host tissue through a breach in the skin produced by local trauma. However, in many patients there is no history of trauma at the site of infection. In areas where mycetoma is endemic the habit of going barefooted is frequent and thorns pricks are plentiful. As a result, natural infection is expected to be more frequent than it actually is, if this theory of route of infection is true. Many workers in the field believe that, there is an intermediate host for the infection but it is not known. Still there are many controversies on the infection susceptibility and resistance.[9,10] The disease is not contagious from one person to another or from animal to human.[1,2,3]

Incubation Period

The incubation period in mycetoma is unknown due to the difficulty in establishing the time of initial infection, however, in experimental animals the formation of the mycetoma lesion was noted after a period of three weeks from the inoculation of the organism.[11]

Clinical Presentation

Mycetoma presents as a slowly progressive, painless, subcutaneous swelling commonly at the site of previous trauma. The swelling is usually firm and rounded but it may be soft, lobulated, rarely cystic and is often mobile.[12] Multiple secondary nodules may evolve; they may suppurate and drain through multiple sinus tracts. The sinuses may close transiently after discharge during the active phase of the disease. Fresh adjacent sinuses may open while some of the

old ones may heal completely. They are connected with each other, with deep seated abscesses and with the skin surface. The discharge is usually serous, sero-sanguinous or purulent. During the active phase of the disease the sinuses discharge grains, the colour of which depends on the causative organism. The grains can be black, yellow, white or red and they are of variable size and consistency.[13,14]

Mycetoma is usually painless in nature which is an important cause for the late presentation of most patients. It was suggested that, mycetoma produces substances that have an anaesthetic action. Pain may be produced by the expansion of the bone with the mycetoma granuloma and grains but it is more commonly due to secondary bacterial infection. [1,2,15]

As the mycetoma granuloma increases in size the skin over it becomes attached and stretched. The skin may become smooth and shiny. Areas of hypo or hyper-pigmentation sometimes develop. In some patients there may be areas of local hyperhidrosis over the mycetoma lesion. The explanation of this phenomenon is unclear; it may be due to sympathetic over-stimulation or increased local temperature due to increased arterial blood flow caused by the chronic inflammation. [6,7,16,17]

Mycetoma eventually invades the deep structures. This is usually gradual and delayed in eumycetoma while in actinomycetoma, it is earlier and extensive. For unknown reasons, the tendons and the nerves are curiously spared until late in the disease process. This may explain the rarity of neurological and trophic changes even in patients with long standing mycetoma. The absence of the trophic changes may be explained by the adequate blood supply in the mycetoma area.[3,6,16,17]

In the majority of patients, the regional lymph nodes are small and shotty. An enlarged regional lymph node is not uncommon and this may be due to secondary bacterial infection, genuine mycetoma lymphatic spread or may be due to local immune responses to mycetoma.

The infection remains localised and the constitutional disturbances are rare but when they do occur they are generally due to secondary bacterial infection. Cachexia and anaemia may be seen in late mycetoma. This is often due to malnutrition, sepsis and mental depression. Mycetoma can produce many disabilities, distortion and deformity. It can be fatal especially in cases of cranial mycetoma.[17-24]

Mycetoma Site

Mycetoma in general involves those parts of the body that come in contact with soil during daily activities. The foot is the most affected site and this is seen in 70% of patients. Most of the lesions are seen on the dorsal aspect of the forefoot and for unexplainable reasons, the left foot is affected more. The hand is the next commonest site which occurs in 12% of patients. In endemic areas other parts of the body may be involved but less frequently such as the knee, arm, leg, head and neck, thigh and the perineum which are affected in descending order of frequency. Rare sites such as the chest and abdominal walls, fascial bones, mandible, testes, paranasal sinuses and eye may be affected.(Figs.1,2,3,4,5) [1,2,3,17-24]

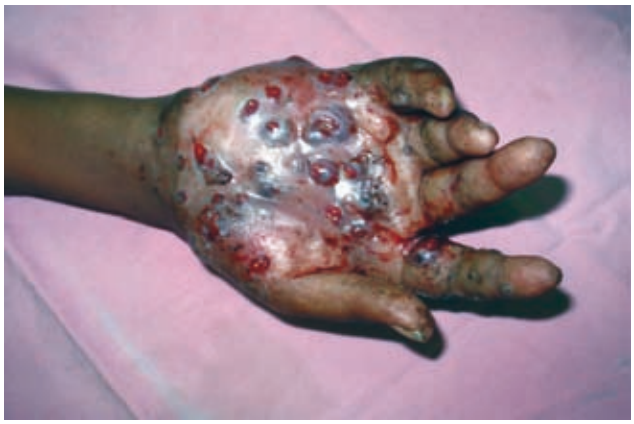

Fig.1: Hand eumycetoma

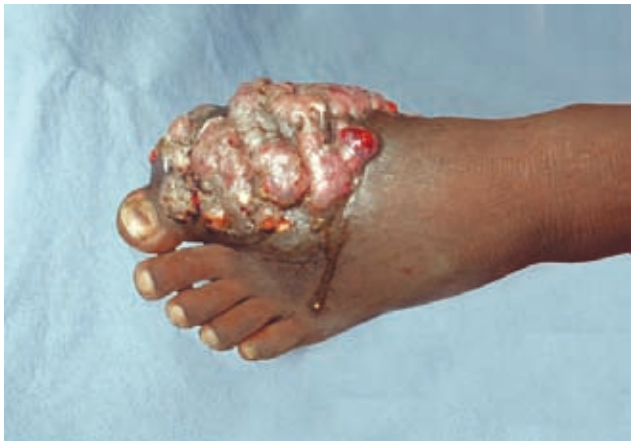

Fig.2: Foot eumycetoma

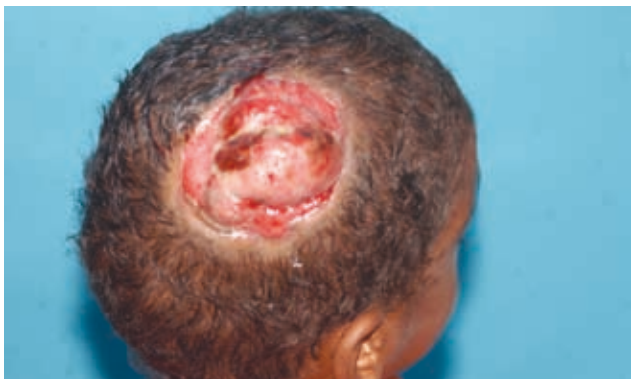

Fig.3: Extensive head eumycetoma with intra-cranial extension

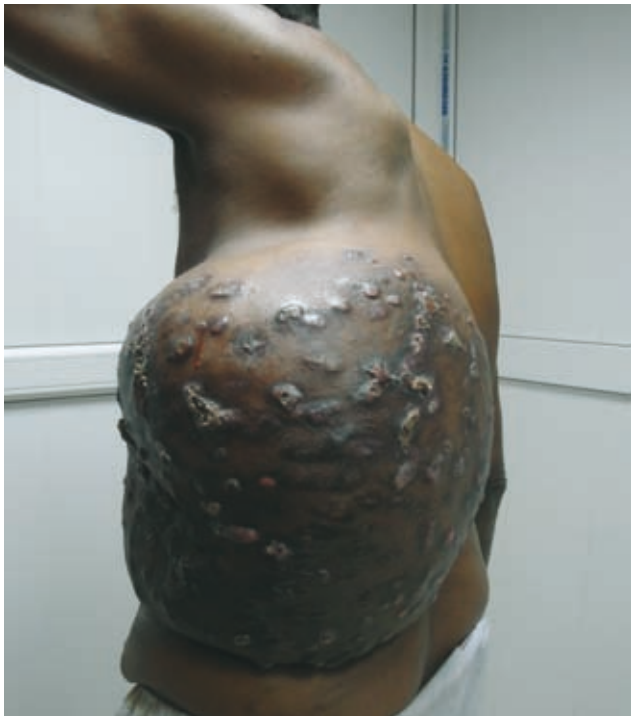

Fig.4: Extensive chest wall eumycetoma

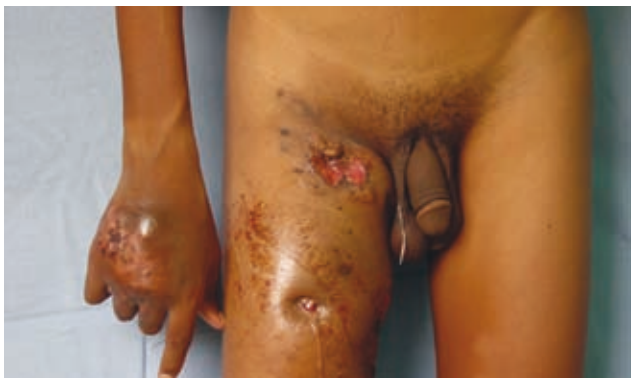

Fig. 5: Multiple hand, inguinal and thigh euycetoma

Spread of Mycetoma

In the subcutaneous tissue the organism multiplies forming colonies which spread along the fascial planes to involve the skin and the underlying structures. It may spread along the lymphatics to the regional lymph nodes. During the active phase of the disease these lymphatic satellites may suppurate and discharge as well. Lymphatic spread is more common in actinomycetoma than in eumycetoma and its incidence is augmented by repeated inadequate surgical excision. There is now strong evidence that, blood borne spread in mycetoma can occur. [1,5,6]

It is worth noting that, the apparent clinical features of mycetoma are not always a reliable indicator of the extent and spread of the disease, as some small lesions with few sinuses may have many deep connecting tracts, through which the disease has spread quite extensively. This is why in mycetoma, surgery under local anaesthesia is contra-indicated. [1,2,3]

Differential Diagnosis

The differential diagnosis of mycetoma includes many soft tissue tumours such as Kaposi's sarcoma, malignant melanoma and fibroma. Thorn and foreign body granuloma must be considered in the differential diagnosis of mycetoma. The presence of bone destruction in the absence of sinuses tends to favour the possibility of tuberculosis. The radiological features of advanced mycetoma are comparable to primary osteogenic sarcoma. Primary osseous mycetoma is to be differentiated from chronic osteomyelitis, osteoclastoma, bone cysts and from syphilitic osteitis. It may be wise to state that, in mycetoma endemic areas, any subcutaneous swelling must be considered as mycetoma until proved otherwise.[1,2,6,7]

Diagnosis of Mycetoma

Many diagnostic tools and procedures are required to confirm the diagnosis of mycetoma, its type and extension. This is vital as proper management depends on accurate diagnosis. ([1,2,3]

Mycetoma Imaging

Several imaging techniques are needed to confirm the diagnosis and these may include, X- Ray, ultrasound, CT scan and MRI.

X-Ray Imaging

In the early stage, there may be a soft tissue granuloma, which is shown as a dense shadow or as scattered multiple soft tissue shadows. Calcification and obliteration of the fascial planes may sometimes be seen. As the disease progresses, the cortex may be compressed from outside by the granuloma leading to bone scalloping. This is then followed by a variable amount of periosteal reaction. Periosteal new bone spicules are laid down at right angles to the cortex to create a sun-ray appearance and Codman triangle; an appearance that may be indistinguishable from that of primary osteogenic sarcoma. Late in the disease, there may be multiple punched out cavities throughout the bone. These cavities are large in size, few in number with well-defined margins in eumycetoma. Whereas, in actinomycetoma they are usually smaller in size, numerous and have no definite margins. The cavities are usually filled with solid masses of grains and fibrous tissue, which provides bone support. This may explain the rarity of pathological fractures in mycetoma. The bony changes in the skull are unique; they are purely sclerotic with dense bone formation and loss of trabeculation. The cause of this is unclear. (6.7,25)

Osteoporosis at and distal to the affected part is well observed in mycetoma and this may be due to disuse atrophy. Chemotherapy causes radiological improvement consisting of remoulding, absorption of the sclerotic bone and reappearance of the normal trabecular pattern.(Fig.6) (25,26,27,28,29)

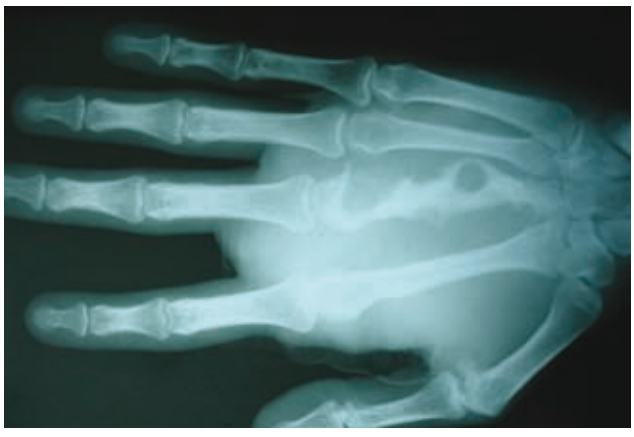

Fig.6: Hand x-ray showing typical eumycetoma features

Ultrasonic imaging of Mycetoma

The mycetoma grains, its capsule and the accompanying inflammatory granuloma have characteristic ultrasonic appearances. Ultrasound imaging can differentiate between eumycetoma and actinomycetoma as well as between mycetoma and other conditions. In eumycetoma lesions, the grains produce numerous sharp bright hyper-reflective echoes, which are consistent with the grains. The grain cement substance is most probably the origin of these sharp echoes. In addition, there are multiple thick walled cavities with absent acoustic enhancement. In actinomycetoma lesions, the findings are similar but the grains are less distinct. This may be due to their smaller size and consistency, individual embedding of the grains or the absence of the cement substances in few of them.(30)

The size and extent of the lesion can be accurately determined ultrasonically and this is useful in planning surgical incisions and procedures. The technique is safe, simple and can be done as an out-patient procedure.(Fig. 7)(30)

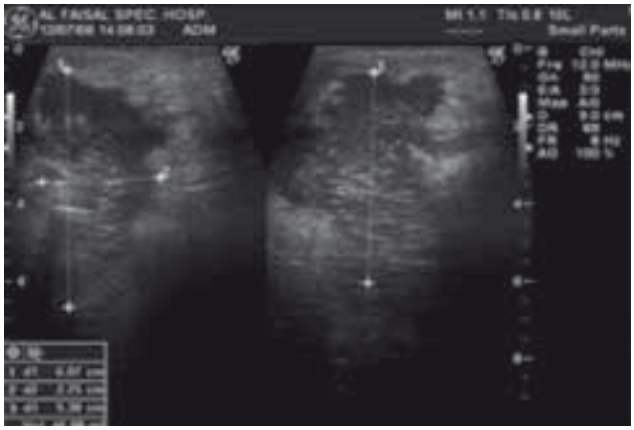

Fig.7:Ultrasound showing typical features of eumycetoma

Mycetoma MRI

MRI of mycetoma lesions is helpful in visualization of the extension of bone destruction, periosteal reaction and soft tissue involvement. It is sensitive for assessing the extent of mycetoma in the soft tissues. MRI usually shows multiple 2-5 mm lesions of high signal intensity, which indicates the granuloma, interspersed within a low-intensity matrix which is the fibrous tissue. The “dot-in-circle sign”, which indicates the presence of grains, is characteristic of

mycetoma and it is highly specific. The differential diagnosis of mycetoma MRI is chronic osteomyelitis, granulomas, soft tissue tumours, bone tuberculosis and cold abscesses.(Fig.8)[6]

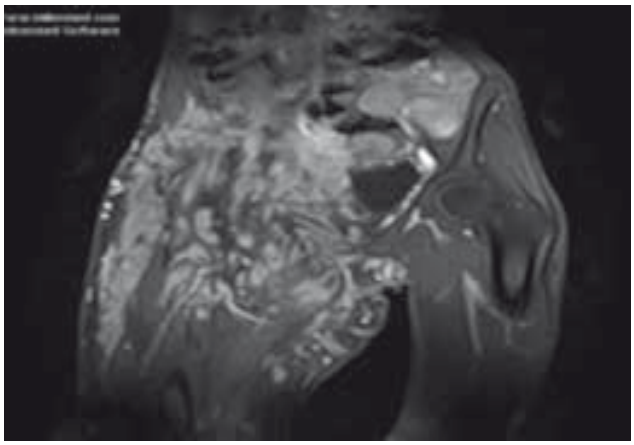

Fig.8: Mycetoma MRI showing features of mycetoma

Mycetoma CT Scan

CT findings in mycetoma are not specific but are helpful to detect early bone involvement.

Histopathological Diagnosis

Histological examination in mycetoma is attractive as it requires neither aseptic techniques nor rigid time schedule but they lack the precision of culture. It always needs surgical biopsy which should be a deep biopsy done under general or regional anaesthesia. The chance of local spread with the surgical biopsy is high. The biopsy should be adequate and contains grains. It should be fixed immediately in 10% formal -saline.[6,29]

Various stains can be used in the microscopic identification of the causative organism and the host tissue reaction. Haematoxylin and eosin (H&E) stain is the commonest stain in use. Immuno-fluorescent antibody and immuno-histochemistry techniques can be used to improve the histological identification of the organisms and host reactions.[6]

Three types of host tissue reaction against the organism were described and they are identical in all types of mycetoma.

In Type I tissue reaction, the grains are usually surrounded by a layer of polymorphonuclear leucocytes. The inner most neutrophils are closely attached to the surface of the grain. They sometimes invade the grain causing its fragmentation. The hyphae and cement substance disappear and only remnants of brown pigmented cement are left behind.

Outside the neutrophils zone there is granulation tissue containing macrophages, lymphocytes, plasma cells and few neutrophils. The mononuclear cells increase in number towards the periphery of the lesion. The outermost zone of the lesion consists of fibrous tissue. (31-34)

In Type II tissue reaction, the neutrophils largely disappear and are replaced by macrophages and multinucleated giant cells. The latter engulf grain material. This consists largely of pigmented cement substance although hyphae are sometimes identified. Other inflammatory cells and histological changes are the same as in type I reaction.

Type III reaction, is characterised by the formation of a well-organized epithelioid granuloma with Langhan's type of giant cells. The centre of the granuloma sometimes contains remnants of fungal material but in some no fungal elements could be identified. Inflammatory and histological changes are the same as described for both type I and II reactions.(Fig.9)

(1-34)

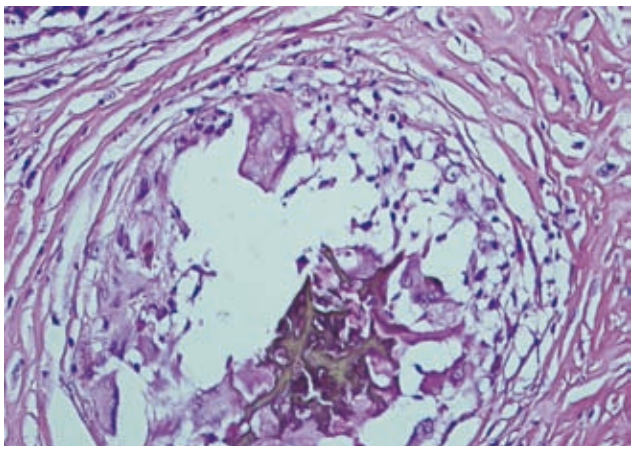

Fig.9: type I and II tiusse reactions

Fine Needle Aspiration Cytology of Mycetoma

Mycetoma can be accurately diagnosed by Fine Needle Aspiration (FNA) cytology and cell block technique. Mycetoma lesions have a distinct appearance in a cytology smear typical to that seen in histopathological sections. FNA allows morphological identification of mycetoma and its classification into eumycetoma and actinomycetoma. The technique is simple, rapid, sensitive and can be tolerated by patients.[35,36]

Causative Organisms Culture

A large variety of microorganisms can produce mycetoma.[4,37] These microorganisms can be identified by their textural description, morphological and biological activities in pure culture. Deep surgical biopsy is always needed to obtain the grains. The grains are the culture source and they should be viable and free of contaminants. The grains extracted through the sinuses are usually contaminated and not viable and hence should be avoided. Several media may be used to isolate and grow these organisms. The media may or may not contain antibiotics. Malt extract, Sabouraud's and Glucose nutrient agars are the commonest types of media used in cultures of Mycetoma organisms.

The culture technique is cumbersome and time consuming with chance contamination happening which may give a false positive result. It also requires experience to identify the causative organisms. [3,5,6]

Mycetoma PCR Identification

Molecular detection and identification of the causative organism is important to understand the disease aetiology, epidemiology and organisms taxonomy, which ultimately improves patients' care. A specific PCR test amplifying a region of the internal transcribed spacer in the ribosomal gene complex is now available.[38]

Serodiagnosis in Mycetoma

In the absence of the classical triad of mycetoma, the demonstration of significant antibodies titres against the causative organism may be of diagnostic value and for patients follow up. The common sero-diagnostic techniques in use are counter-immuno-pheresis and ELISA. These tests are tedious, need purified antigens and hence it is time consuming with cross reactivity between the different organisms commonly occurring[1,2,3]

Management of Mycetoma

The treatment of mycetoma depends mainly on its aetiological agent and the site and extent of the disease. Until recently, the only available treatment for mycetoma was amputation or multiple mutilating surgical excisions. No case of self-cure has ever been reported in the medical literature. However, spontaneous lesion regression was observed in some patients. Combined medical and surgical treatment is the gold standard in mycetoma. This regime facilitates surgery, accelerates healing and reduces the chance of relapse.[39,40.41]

The Treatment of Actinomycetoma

In general, actinomycetoma is amenable to medical treatment with antibiotics and other chemotherapeutic agents. Combined drug therapy is always recommended to avoid drug resistance and for disease eradication.

Many reports showed excellent clinical response to the combination of Amikacin Sulfate and Co-tri-moxazole. They are given in a form of cycles; each one consists of Amikacin Sulfate in a dose of 15 mg/kg twice daily for three weeks and Co-tri-moxazole in a dose of 1.5 mg/kg twice daily for five weeks; the cycles are repeated till cure.The number of cycles ranges between five and ten cycles. Renal failure and oto-toxicity are well recognised complications.[38,39]

Many other drugs such as Amoxicillin-Clavulanic Acid, Rifampicin, Sulphonamides, Gentamicin, and Kanamycin were tried as a second line of treatment for actinomycetoma in patients who did not respond to the first line treatment or who developed serious drug side effects. However, these drugs take a long time to achieve cure, the mean duration is around one year and the recurrence rate was high. They have many side-effects and some of these are serious such as Stephen Johnson syndrome.[39,40]

Treatment of Eumycetoma

The most popular medical treatment regimes for eumycetoma are 400-800 mg/day Ketoconazole, 200-400 mg/day Itraconazole or 300-400 mg/day Voriconazole for extended periods with a mean duration of nine to twelve months. These drugs

have many serious side-effects. The side effects are more noticeable with Ketoconazole and these include hepatotoxicity, gynaecomastia, lip dryness and ulceration, skin darkness and decreased libido. These drugs are contra-indicated during pregnancy and lactation. Ketoconazole and Itraconazole are not curative in most eumycetoma patients; they help in localizing the disease by forming well localized, thickly encapsulated lesions which are easily excised surgically.[41] There are many clinical trials and laboratory studies going on for more effective drugs for the treatment of eumycetoma. [42-47]

Medical treatment for both types of mycetoma must continue until the patient is clinically, radiologically, ultrasonically and cytologically cured. Cure is considered when the skin becomes normal, the mass disappears, the sinuses heal, and the organisms are eliminated from the tissue. Clinical improvement is judged by reduction in the size of the mass and healing of most of the sinuses. [6]

Radiological examination is an essential tool for follow up of patients on medical treatment. It usually shows reappearance of normal bone pattern and the disappearance of the soft tissue mass. Absent grains cytologically with type III tissue reaction and the disappearance of the grains and cavities ultrasonically are reliable evidences for cure. [1,6]

Surgery for Mycetoma

Surgery is indicated in mycetoma for small localized lesions, resistance to medical treatment or for better response to medical treatment in patients with massive disease. The surgical options range from wide local and debulking excisions to amputations. Amputation is indicated in advanced mycetoma not responding to medical treatment with severe secondary bacterial infection and it can be a life saving procedure. The amputation rate ranges from 10-25% in most series. [1,6]

Diagnostic surgical procedures are indicated to obtain tissue biopsy for histo and immuno-histo-chemical studies and grains for microbiological and molecular identification.

Local anaesthesia is contra-indicated in mycetoma as the disease extension along tissue planes is usually massive and un-predictable. A bloodless operative field using a tourniquet is mandatory to identify the lesion margins to avoid bursting, which will facilitate local disease spread. The latter is an important cause of recurrence. Fig.10 [1,2,3,40]

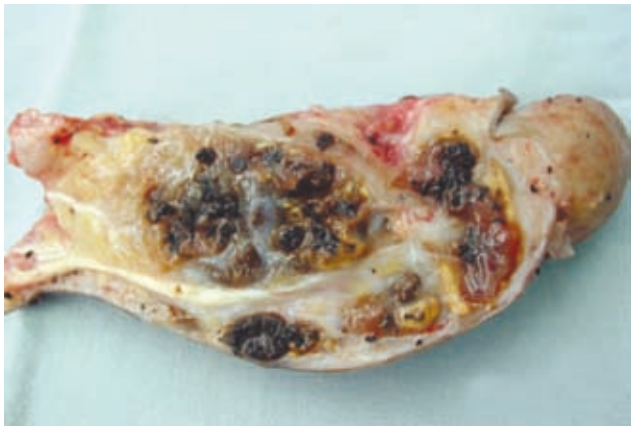

Fig. 10: Surgical specimen showing extensive fibrosis & multiple grains

Recurrence in mycetoma

The postoperative recurrence rate varies from 25 to 50% and this can be local or distant at the regional lymph nodes. This could be due to the disease biology and behaviour, inadequate surgical excision due to the use of local anaesthesia and lack of surgical experience and drug compliance due to financial reasons and/or lack of health education.[1,2,40]

Mycetoma surgery should be regarded seriously as the extent of the lesion is often much more than what its appearance suggests. Post-operative medical treatment is essential because if the treatment is stopped after apparent cure, recurrence may be immediate. Follow up of patients with mycetoma must be long enough to detect early recurrence and to advise early treatment. [1,2,40]

Conclusions

The morbidity caused by mycetoma is massive and enormous. It has many clinical and socio-economic impacts on patients, families and the community. In areas where mycetoma is endemic, local health care facilities and health education are usually insufficient and inadequate. Mycetoma is a hard-to-treat disease in many tropical and subtropical regions due to multifactorial reasons.

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