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Mycetoma: a thorn in the flesh☆

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Summary Mycetoma is a chronic, granulomatous, subcutaneous, inflammatory disease caused by true fungi (eumycetoma) or filamentous bacteria (actinomycetoma). It occurs in the mycetoma belt stretching between the latitudes of 15° South and 30° North and is endemic in relatively arid areas. The organisms are present in the soil and may enter the subcutaneous tissue by traumatic inoculation. Mycetoma commonly affects adults aged 20 to 40 years, predominantly males. The foot is most commonly affected. Both forms of mycetoma present as a progressive, subcutaneous swelling, although actinomycetoma has a more rapid course. Multiple nodules develop which may suppurate and drain through sinuses, discharging grains during the active phase of the disease. Diagnosis may involve radiology, ultrasonic imaging, cytology, culture, histology or immunodiagnosis. Actinomycetoma is amenable to treatment by antibiotics, preferably by combined drug therapy for long periods. Eumycetoma is usually treated by aggressive surgical excision combined with medical treatment.

1. Introduction

Mycetoma is a serious health problem in many tropical and sub-topical subcontinents. It has many medical, social and economic impacts both on patients and the community. Mycetoma is a chronic, specific, granulomatous, progressive subcutaneous inflammatory disease. The disease is caused by true fungi or by filamentous bacteria and hence it is classified into eumycetoma and actinomycetoma respectively. Painless subcutaneous swelling, sinus tract formation and discharge that contain grains are pathognomic of mycetoma (Fahal and Hassan, 1992).

2. Epidemiology

Due to various reasons, the true incidence of mycetoma throughout the world is not precisely known. Mycetoma has a worldwide geographical distribution but this is extremely uneven. It occurs in what is known as the mycetoma belt stretching between the latitudes of 15° South and 30° North. The belt includes Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Colombia, Argentina and others (Mahgoub and Murray, 1973). Mycetoma has been reported in some temperate regions as well (Magana, 1984).

The geographical distribution of the individual mycetoma organisms shows significant variations, which can be convincingly explained on an environmental basis. Areas where mycetoma is endemic are relatively arid zones with a short rainy season with a low relative humidity (Gonzalez-Ochoa, 1975).

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The organisms are usually present in the soil in the form of grains. Traumatic inoculation of the subcutaneous tissue caused by sharp objects such as thorn pricks, or splinters is thought to be the route of entry. However, this theory has been recently disputed, as many patients have no history of trauma at the infection site. In areas where mycetoma is frequent the habit of going barefoot is common and thorns are plentiful and as result, natural infection is expected to be more frequent than it actually is. Mycetoma in deep tissues without skin involvement is frequently reported. Furthermore, the isolation of the causative organisms from the soil is difficult; all these suggest that, the presence of an intermediate host is important to produce infection in man (Ahmed et al., 2002). The disease is neither contagious from person to person, nor from animal to human.

3. Clinical presentation

Male predominance is a constant finding in mycetoma with a sex ratio of 3.7:1. This is commonly attributed to the greater risk of exposure to organisms in the soil during outdoor activities (Abbott, 1965). However in some areas where mycetoma is endemic females are more committed to outdoor activities than males. It is interesting to note that during pregnancy mycetoma become more active and aggressive. Change in hormonal environment and decreased immune response during pregnancy may be the explanation for this observation. No age is exempt but mycetoma commonly affects adults between 20—40 years of age and these are the most active members of the society especially in underdeveloped countries (Fahal and Suliman, 1994). Mycetoma is seen more conventionally in farmers, field workers and in herdsmen, in endemic areas people of other occupations are also affected.

The clinical presentation of mycetoma is identical in both types. However, actinomycetoma has a rapid progressive course compared to eumycetoma. In the latter, the lesion grows slowly with clear defined margins and remains encapsulated for a long period, whereas, in actinomycetoma the lesion is more inflammatory, more destructive and invades the bone at an earlier period. Mycetoma presents as a slowly progressive painless subcutaneous swelling, which is usually firm and rounded but it may be soft, lobulated, rarely cystic and it is often mobile (Fahal et al., 1998). Multiple secondary nodules then develop; the nodules 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 older ones may heal completely. They are connected with each other, with deep sterile abscesses and with the skin surface. The discharge is usually serous, serosanguinous 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. Pus, exudate, the dressing gauze and biopsy material should be examined for the presence of the grains.

Mycetoma is usually painless in nature. It has been suggested that the mycetoma produces substances that have an anaesthetic action (Gumaa, 1983) or that the lack of pain may be due to nerve damage at a later stage of the disease. Pain may be produced by the expansion of the bone by the mycetoma granuloma and grains or it may be due to secondary bacterial infection (Gumaa, 1983).

Skin changes are common in mycetoma. In some patients, there may be areas of local hyperhidrosis confined only to the mycetoma lesion and the skin around it; the reason for this is unclear. For unknown reasons, the tendons and the nerves are curiously spared until very 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 trophic changes may also be explained by the adequate blood supply in the mycetoma lesion. (Fahal et al., 1997).

In the majority of patients, the regional lymph nodes are small and shotty. Regional lymph adenopathy is not uncommon. This may be due to secondary bacterial infection, genuine lymphatic spread of mycetoma or it may be due to immune complex deposition as part of a local immune response to mycetoma infection (El Hassan and Mahgoub, 1972).

The infection remains localised and constitutional disturbances are rare but when they do occur, they are generally due to septiacemia or to immuno-suppression. 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 if it affects the skull (Gumaa et al., 1986).

4. Mycetoma site

The foot is affected most often (80% of cases) in mycetoma. The lesions are seen commonly on the dorsal aspect of the forefoot and for unexplained reasons the left foot is affected more than the right. The hand ranks as the second commonest site

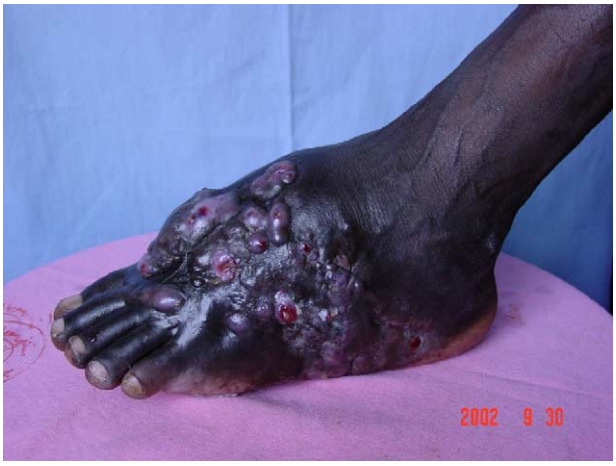


Fig. 1 Advanced mycetoma of the foot. Note the swelling, deformity and sinuses.

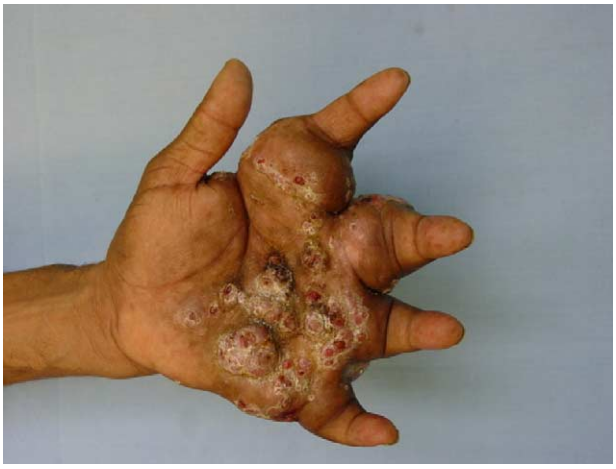


Fig. 2 Hand mycetoma.

(6.6%), the right hand is more often affected (Fahal and Suliman, 1994; Fahal et al., 1994; Mahgoub, 1985). In endemic areas other parts of the body may be involved but less frequently and these include the knee, arm, leg, head and neck, thigh and the perineum. Rare sites such as the chest and abdominal walls, fascial bones, mandible, paranasal sinuses, eyelid, vulva, orbit, scrotum and surgical incisions may be affected (Fahal et al., 1996) (Figs. 1 and 2).

5. Spread of mycetoma

In the subcutaneous tissue the organism multiplies forming colonies that spread along the fascial planes to involve the skin, subcutaneous fat and then the underlying structures. The nerves and tendons are rarely affected until late in the disease course. In about 1—3% of cases there is genuine lymphatic spread to the regional lymph nodes. During the active phase of the disease these regional lymphatic foci 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 (El Hassan and Mahgoub, 1972). There is no report of blood-borne spread in mycetoma.

6. Differential diagnosis

Many soft tissue tumours such as lipoma, fibroma, fibrolipoma, sarcomas, malignant melanoma as well as thorn and foreign body granulomas resemble mycetoma clinically. Osteogenic sarcoma and bone tuberculosis have radiological features similar to advanced mycetoma (Fahal and Hassan, 1992). Primary osseous mycetoma has a radiological appearance like chronic osteomyelitis, osteoclastoma, bone cysts and syphilitic osteitis.

7. The diagnosis of mycetoma

7.1. Radiology

In early mycetoma lesions, there is a soft tissue granuloma, which is shown as a dense shadow or as multiple scattered 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 followed by a variable amount of periosteal reaction. Periosteal new bone spicules are laid down at right angle to the cortex to create a sun-ray appearance and Codman triangle, an appearance that may be indistinguishable from that due to osteogenic sarcoma. Late in the disease, there may be multiple cavities. They are large in size, few in number with well-defined margins in eumycetoma (Fig. 3), whereas, in actinomycetoma, they are usually smaller in size, numerous and have no definite margins (Abbott, 1965; Davies, 1958). The cavities are produced by the replacement of the osseous tissue by the grains. Their size is due to the size of the grains of the causative organism. 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 (Fahal et al., 1996; Abd Bagi et al., 2003). The bony changes in the skull are unique: they are purely sclerotic with dense bone formation and loss of trabeculation.

Due to the disuse atrophy and compression of the bone and its blood supply by the mycetoma

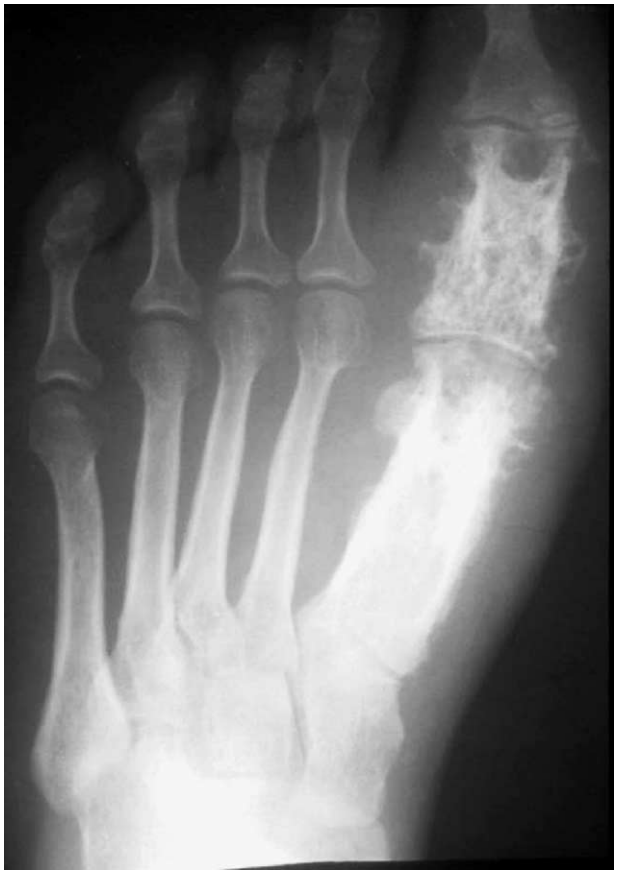


Fig. 3 X-ray foot showing massive soft tissue mass, periosteal reaction and bone destruction.

granuloma, osteoporosis is well recognised in advanced mycetoma. With chemotherapy bone changes in the form of remoulding, absorption of the sclerotic bone and reappearance of the normal trabecular pattern are observed, hence radiological follow-up of patients is essential to ascertain cure.

7.2. Ultrasonic imaging of mycetoma

The mycetoma grains, the capsule and the accompanying inflammatory granuloma have characteristic ultrasonic appearances. Ultrasound imaging can differentiate between eumycetoma and actinomycetoma and between mycetoma and other non-mycetomous lesions. In eumycetoma lesions, the grains produce numerous sharp bright hyperreflective echoes, which are consistent with the black grains. The grain cement substance is most probably the origin of these sharp echoes. Also there are multiple thick-walled cavities with absent acoustic enhancement. In actinomycetoma lesion, 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 (Fig. 4).

The ultrasonic diagnosis of mycetoma is more precise and accurate in lesions with no sinuses. The size and extent of the lesion can be accurately determined ultrasonically and this is useful in planning surgical incisions and procedures (Fahal et al., 1997).

7.3. Fine needle aspiration cytology of mycetoma

Mycetoma can be accurately diagnosed by fine needle aspiration (FNA) cytology (El Hag et al., 1996). Mycetoma lesion has a distinct appearance in a cytology smear and is characterised by the presence

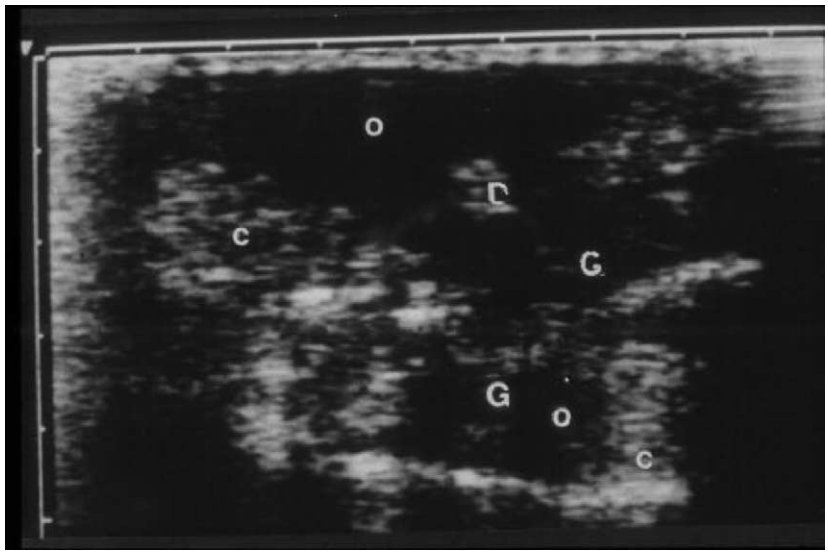


Fig. 4 Ultrasonic examination showing, numerous sharp bright hyperreflective echoes, which are consistent with the black grains G. There are multiple thick walled cavities with absent acoustic enhancement C.

of polymorphous inflammatory cells consisting of an admixture of neutrophils, lymphocytes, plasma cells, histiocytes, macrophages and foreign body giant cells and grains. In sections, the grain is closely surrounded by and occasionally infiltrated by neutrophils causing its fragmentation. Outside the neutrophil zone, monocytic cells and giant cells are seen. This is surrounded by granulation tissue rich in fibroblasts. Different grains have distant appearance, which allows morphological identification and classification of mycetoma (Fig. 5).

The technique is simple, cheap, rapid and sensitive and it is tolerated by patients. It can be used in routine diagnosis and as an effective means of collection of material for culture and immunological studies. Due to the simplicity of the technique it can be used in epidemiological survey of mycetoma and for detection of early cases in which radiological and serological techniques may not be helpful.

7.4. Culture

A large variety of microorganisms are capable of producing mycetoma. They can be identified by their textural description, morphological and biological activities in pure culture. The biological activity may include, acid fastness, optimal temperature, proteolytic activity, utilization of sugars and nitrogenous compounds (Rippon, 1988). The grains are the source of the culture and they should be alive and free of contaminants. Many culture media are in use e.g. Sabouraud, blood agar and malt extract agar. The culture technique is often cumbersome, time consuming and chance contamination may give a false positive result. It also requires experience to identify the causative organisms.

7.5. Histology

Stained sections usually show the grain morphology and the tissue reaction to the organisms. Three types of tissue reactions have been described. (Fahal et al., 1995).

7.5.1. Type I reaction

In Type I 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 substance of the grain causing its fragmentation. The hyphae and cement substance usually disappear and only remnants of brown-pigmented cement are left behind.

Outside the zone of neutrophils there is granulation tissue containing macrophages, lymphocytes, plasma cells and few neutrophils. The mononuclear cells increase in number towards the periphery of the lesion (Fig. 6). Many of the macrophages have plentiful vacuolated cytoplasm. Some macrophages are phagocytising nuclear debris and neutrophils. The vacuolated macrophages give a positive reaction for lipid and Russell's bodies are observed. Capillaries and venules are surrounded by concentrically arranged layers of fibrin giving them an onion skin appearance. The outermost zone of the lesion consists of fibrous tissue. The arterioles show hypertrophied muscles. The intima is thickened and oedematous and the lumen is narrowed, the nerves showed oedema and sometimes a mononuclear cell infiltrate. Some of the sweat glands may show hypertrophy and hyperplasia.

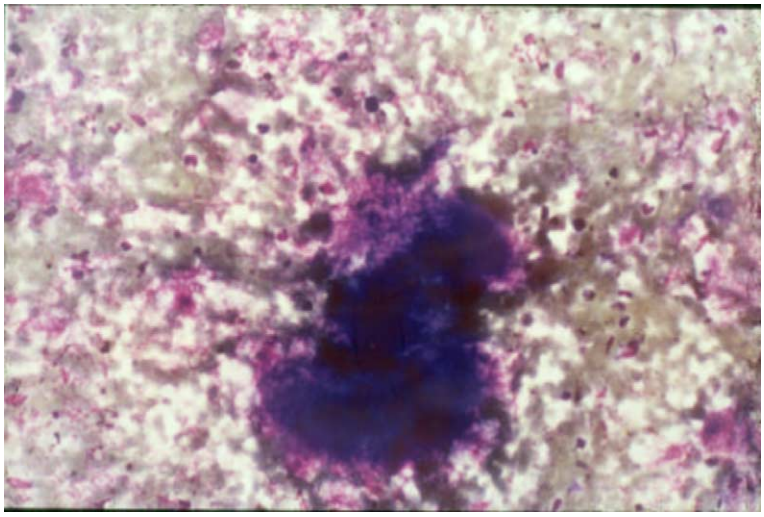


Fig. 5 Microphotograph showing *A. peletteri* grain in a cytological smear.

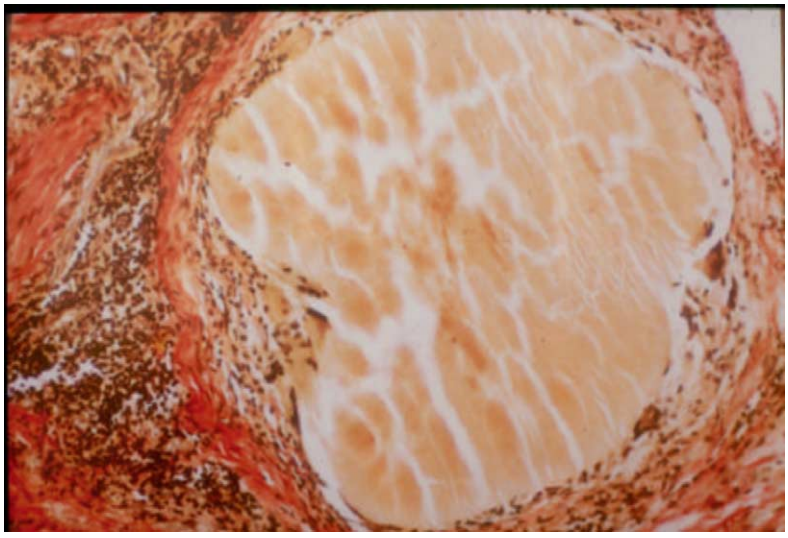


Fig. 6 Microphotograph of *S. somaliensis* with Type I tissue reaction.

7.5.2. Type II reaction

The neutrophils have largely disappeared and are replaced by macrophages and multinucleated giant cells. The latter have engulfed 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 (Fig. 7).

7.5.3. Type III reaction

At this stage there is formation of a well-organized epithelioid granuloma with Langhans's giant cells. The centre of the granuloma sometimes contains remnants of fungal material but in some no fungal elements can be identified. Inflammatory and histological changes are the same as described for both types I and II reactions (Fig. 8).

7.6. Immunodiagnosis of mycetoma

Recently the immune responses in mycetoma lesions caused by *Streptomyces somaliensis* were characterized by immunohistochemistry (El Hassan et al., 2001). In the haematoxylin and eosin sections, the inflammatory reaction around the grain was of two types. In type I there were three zones: a neutrophil zone immediately around the grain, an intermediate zone containing mainly macrophages and a peripheral zone consisting of lymphocytes and plasma cells. By immunohistochemistry, zone 1 stained positive for CD 15 (neutrophils), zone 2 was positive for CD68 (macrophages) and CD3(T lymphocytes) while zone 3 contained CD20+ cells (B lymphocytes). In type II reaction there was no neutrophil zone, the grains being surrounded by

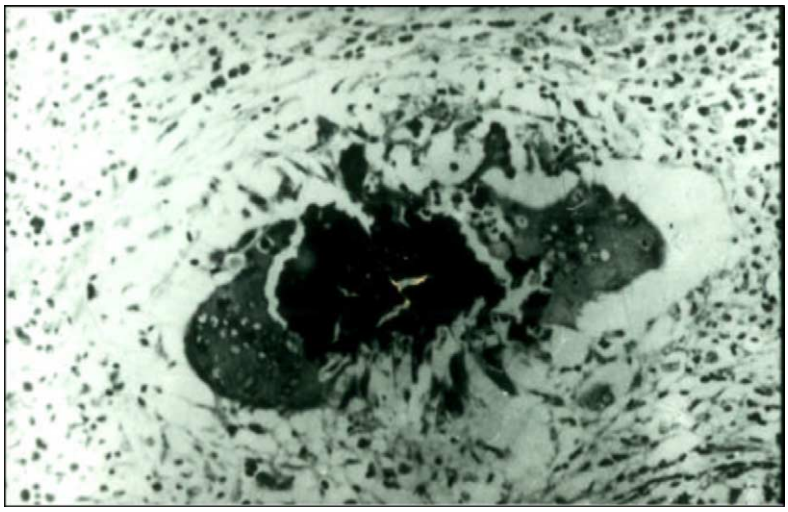


Fig. 7 Microphotograph of mycetoma grain with Type II tissue reaction.

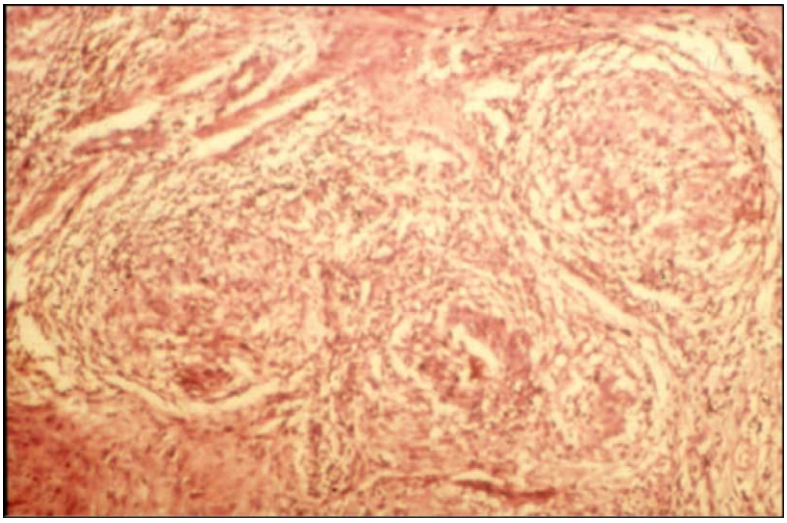


Fig. 8 Microphotograph of Type III tissue reaction.

macrophages and giant cells. This was confirmed by immunohistochemistry, which also showed the presence of CD3+ cells. IgG, IgM and complement were demonstrated on the surface of the grain and on the filaments inside the grain. Neutrophils and macrophages are recruited in the lesion by complement and are involved in the damage of the grain. The cytokine profile in the lesion and regional lymph nodes was of a dominant Th2 pattern (IL-10 and IL-4).

7.7. Serodiagnosis in mycetoma

The demonstration of significant antibodies titres against the causative organism may be of diagnostic value. Serodiagnosis is of a great help in identification and classification of the various organisms, which is an essential prerequisite for medical treatment, and is mandatory for the follow-up of these patients. It has many advantages over culture and histopathological techniques, as both require surgical biopsy, which may enhance the spread of the organism. The common serodiagnostic tests for mycetoma are the immunodiffusion and counter-immuno-electrophoresis (Gumaa and Mahgoub, 1973; Gumaa and Mahgoub, 1975).

Unless antigens used in these tests are quite pure, the tests can be negative in early cases. Cross-reactivity between actinomycetes is quite common and this limits the value of these tests in the diagnosis of the different types of actinomycetes. However these tests and their antigens preparation take a considerable time. Sero-epidemiological survey could give valuable information on the distribution and prevalence of exposure to mycetoma (Taha, 1983).

8. Experimental animals in mycetoma

Few investigators were successful in developing an animal model for mycetoma, but a reproducible animal model has not been reported until recently. Different types of Balb/c mice were infected with various inocula of *M. mycetomatis* mycelia suspended in sterilized soil, as a natural adjuvant, and different routes of infection were used. Most of the animals developed typical mycetoma lesions both in the subcutaneous and intra-abdominal regions, the infection was inoculum dependent and immuno-compromised animals were more susceptible to the infection but had higher mortality. This animal model can be used to study disease pathogenesis and for drug trials. (Ahmed et al., 2003).

9. The management of mycetoma

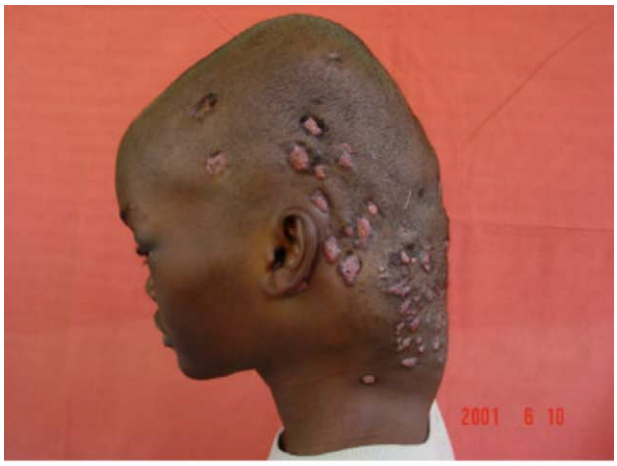
The treatment of mycetoma depends mainly on its aetiological agent and the severity of the disease. Until recently the only available treatment for mycetoma was amputation or mutilating surgical excision of the affected part. No case of self-cure has ever been reported in the medical literature.

9.1. Treatment of actinomycetoma

Actinomycetoma is amenable to medical treatment with antibiotics and other chemotherapeutic agents. Combined drug therapy is always preferred to a single drug to avoid drug resistance and to eradicate residual infection. The common drugs in use include combination of streptomycin sulphate (14 mg/kg daily), diaminodiphenyl sulphone

(dapsone) (1.5 mg/kg twice daily). If there is no response for few months or if there is persistent side effect then dapsone is replaced by co-trimoxazole (14 mg/kg twice daily). An excellent therapeutic response to amikacin sulphate alone or in combination with co-trimoxazole has been reported (Mahgoub, 1972, 1976, 1994; Welsh et al., 1987).

In resistant cases other drugs such as rifampicin, sulfadoxine-pyrimethamine (fansidar) and sulphonamides had been tried. These have proved to be effective in some cases and they remain a good second line therapy. Treatment for mycetoma should be given for long periods and in higher doses as the microorganisms are locked in fibrous tissue. The mean duration of treatment is one year. The cure rate varies between 60% and 90% (Mahgoub, 1972) (Fig. 9a and b).



(a)

(b)

Fig. 9 Patient with head and neck actinomycetoma before (a) and after (b) treatment.

9.2. Treatment of Eumycetoma

In many centres, surgery is still the most acceptable line of treatment for eumycetoma cases. Usually it is in the form of aggressive surgical excision, debulking surgery or amputation in advanced disease (Fahal and Hassan, 1992).

Reports of medical treatment in eumycetoma are few. A few studies showed that, ketoconazole could cure eumycetoma patients. The dose is 300—400 mg daily. The cure rate seemed to be dose dependent. Treatment of these patients may continue for periods ranging from a few months to many years (Mahgoub and Gumaa, 1984). Recently itraconazole was tried in the treatment of patients with eumycetoma, it had a high success and low recurrence rates with few drug side effects. Patients showed a good clinical response to 400 mg itraconazole daily. In these patients, surgical exploration revealed that, the lesions had become well localized and encapsulated with a thick capsule and were easily removed surgically. There seems, no justification for mutilating surgery or amputation prior to giving medical treatment. One disadvantage of these drugs is however, their current high cost.

9.3. Surgery for mycetoma

Surgery in mycetoma is indicated in early localized lesions, for diagnostic proposes, cases resistant to medical treatment or patients with massive mycetoma not responding to repeated long term medical therapy and it can be a life saving procedure. Eumycetoma lesion is well encapsulated and great care must be exercised not to rupture the capsule, which may lead to recurrence by disseminating the grains into other parts of the operative field. Actinomycetoma lesion has an ill-defined border; therefore a margin of healthy tissue should always be excised with the lesion. A bloodless operative field using a tourniquet is mandatory to identify margins of the lesion. It is advisable to flood the wound at the end of surgery with tincture of iodine for elimination of any residual fungal elements.

In advanced cases of mycetoma not responding to medical treatment for a prolonged period amputation is recommended. Extensive repeated excisions of the diseased tissue, including bone, coupled with chemotherapy may be carried out several times to avoid the social consequences of amputation. In less advanced cases less mutilating surgery is advised for example, toe, mid tarsal or Syme's amputation. However, in many cases of inadequate surgery recurrence is inevitable.

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