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MYCETOMA REVISITED

NOWE SPOJRZENIE NA MYCETOMA

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Abstract
Mycetoma or 'Madura foot' is a chronic infection of skin and subcutaneous tissues, fascia and bone. It may be caused by true fungi (eumycetoma) or by filamentous bacteria (actinomycetoma). The lesions are composed of suppurating abscesses and draining sinuses with the presence of grains which are characteristic of the etiologic agents. The introduction of new broad spectrum antimicrobials and antifungals offers the hope of improved drug efficacy. This article discusses the historical aspects, epidemiology, clinical findings, laboratory diagnosis and treatment of mycetoma.

Streszczenie
Mycetoma lub 'stopa madurska' to przewlekłe zakażenie skóry i tkanki podskórnej, powięzi i kości. Może być spowodowane przez grzyby prawdziwe (eumycetoma) lub bakterie nitkowate (actinomycetoma). Zmiany przedstawiają się jako ropiejące wrzody i zatoki z obecnością ziaren, które są charakterystyczne dla tych czynników etiologicznych. Wprowadzenie nowych o szerokim spektrum antybiotyków i leków przeciwgrzybiczych daje nadzieję na poprawę skuteczności leczenia. W tym artykule omówiono aspekty historyczne, epidemiologię, objawy kliniczne, diagnostykę laboratoryjną i leczeniu mycetoma.

Key words: mycetoma; Madura foot; actinomycetoma; eumycetoma
Słowa klucze: mycetoma; stopa madurska; actinomycetoma; eumycetoma

Introduction

Mycetoma is a localized chronic, suppurative and deforming granulomatous infectious disease of subcutaneous tissue, skin and bones, that is present worldwide and is endemic in tropical and subtropical regions. Mycetoma is a pathological process in which the causative agents – a fungus (eumycetoma) or a bacterium (actinomycetoma) from an exogenous source produce grains. Since the treatment of these two etiologies is entirely different, a definite diagnosis after histopathological and microbiolological examination is mandatory. The disease is notoriously difficult to treat. Treatment consists of long courses of antifungals and antibacterials often combined with surgery.

Historical aspects

Gill, who worked at a dispensary in the southern province of Madura, first recognized mycetoma as a disease entity in 1842 [1]. The condition had been known there for many years. Godfrey first documented a case of mycetoma in Madras, India. Native people of the province commonly called the disease as 'Madura foot'. It was Vandyke Carter, who studied the condition over a period of of several years from 1860-1874 and established the fungal etiology of this disorder. He proposed the term 'Mycetoma', literally meaning fungal tumor for the condition, since he found it could also effect other parts of the body than the foot [1]. He classified his cases by the colour of the grains found in the sinus tracts as pale or white, black or red. Pinoy in 1913 recognized the possibility of classifying the cases of mycetoma by grouping the causative organisms, and in 1916 Chalmers and Archibald reviewed the reported cases and published such a classification dividing them into two groups [2,3]:

Group 1 - Maduramycosis, caused by true fungi exhibiting septate filaments usually with chlamydospores and;

Group 2 - Actinomycosis, caused by delicate non-septate filaments of the Actinomyces which belong to higher bacteria.

Epidemiology

Mycetomas are mainly but not exclusively found in the dry tropics where there is a low annual rainfall. It is a disease of poverty, most commonly

affecting agricultural workers and people who are habitually barefoot. The species causing mycetoma vary from country to country and agents that are commoner in one region, are rarely seen in others. Actinomycete Streptomyces somaliensis is isolated most often from from patients originating from Sudan and the Middle East. In India, actinomycotic mycetoma is more commonly encountered than eumycotic mycetoma [4]. However, eumycotic mycetoma accounts for the majority of cases reported from the northern region [5].

Men are more commonly affected than the women and the maximal incidence is seen in the age group of 21-40 years. Since it mostly affects young men, it has a socioeconomic effect on the dependent family members.

Pathogenesis

The disease is usually acquired while performing agricultural work. The organisms are implanted subcutaneously, usually after a penetrating injury. It is usual to find any underlying predisposition in patients with mycetoma, and the persistence of the organism after an initial inoculation appears to be related to its ability to evade host defenses through a variety of adaptations such as cell wall thickening and melanin production.

Etiology

Mycetomas may be caused by various species of fungi and bacteria, which occur as saprophytes in soil or on the plants. Actinomycotic mycetoma is caused by aerobic species of actinomycetes belonging to the genera Nocardia, Streptomyces and Actinomadura.

Eumycotic mycetoma is associated with a variety of fungi, the most common being Madurella mycetomatis, Pseudoallescheria boydii and Acremonium species.

Common causative agents of actinomycotic mycetoma:

Agent	Grain colour
Nocardia asteroids	White
Nocardia brasilienses	White
Nocardia otitidiscaviarum	White
Actinomadura madurae	White
Actinomadura pelletieri	Red to pink
Streptomyces somaliensis	White-to-yellow

Common causative agents of eumycotic mycetoma:-

Agent	Grain colour
Madurella mycetomatis	Black to brown
Madurella grisea	Black to brown
Leptosphaeria senegalensis	Black
Curvularia lunata	Black
Neotestidina rosatii	Yellow
Acremonium spp.	White to yellow
Fusarium spp.	White to pale yellow
Scedosporium apiospermium	White to pale yellow

Clinical presentation of the disease

Mycetoma is a chronic suppurative infection of the subcutaneous tissue and contagious bone. The clinical features are fairly uniform, regardless of the organism involved [6,7]. Since trauma favours infection, feet are the most common site for infection and account for almost two-thirds of cases. Other sites include the lower leg, hands, head, neck, chest, shoulder and arms.

Most cases start out as a small, painless, subcutaneous nodule at the site of injury. The nodule over a period of time begins to soften on the surface and ulcerates to discharge a viscous, purulent, seropurulent or serosanguinous fluid containing characteristic granules. The granules vary in size, colour and consistency depending on the etiological species. These grains are the hallmark of mycetoma.

With time papules, pustules and nodules appear which also break down to form draining sinuses appearing on the skin surface. The disease progresses to involve the surrounding tissues which become swollen, indurated and deformed by fibrous tissue reaction and multiple sinus formation. The condition is usually painless, but become very painfull with the involvement of bones or as a result of secondary bacterial infection.

Mycetoma is usually localized but may extend slowly by direct contiguity along the fascial planes, invading the subcutaneous tissue, fat, ligaments, muscles, and bones. In eumycotic mycetoma, there may be multiple punched out lytic lesions in bones. Actinomycotic mycetoma is characterized by both osteolytic and osteosclerotic lesions. The end result is gross swelling of the affected foot or other part with serious deformity.

Complications

The disease causes disfigurement but is rarely fatal. In advances cases, deformities or ankylosis may occur. Chronic neglected infection may necessitate amputation. Immunocompromised patients may develop invasive infection. Lymphatic obstruction and fibrosis may cause lymphoedema. Complications may also result from toxicity due to prolonged antimicrobial or antifungal therapy.

Differential Diagnosis

Mycetoma has to be differentiated from the following:

- Osteomyelitis (bacterial or tubercular)
- Actinomycosis
- Botryomycosis
- Chromoblastomycosis
- Sporotrichosis
- Atypical mycobacterial infection

Laboratory Diagnosis

Clinical material:

Serosanguinous fluid or seropurulent fluid, scrapings of sinuses, tissue biopsy or excised sinus should be examined for the presence of grains. Saline dressings applied overnight over the swelling can also be observed for the presence of grains. The grains discharged from the sinuses vary in size, colour and consistency, features used for the rapid provisional identification of the etiological agent [8,9].

Direct microscopy:

A Gram stain is of considerable value in distinguishing between actinomycetoma and eumycetoma. The fine branching filaments, only about 1 micron thick, within the grains of actinomycetoma are gram-positve. The grains of eumycetoma are gram negative [10,11]. The filaments and hyphae of the causal agent can be stained better in biopsy samples with Gram

stain (actinomycetoma) or Gomori methamine silver or periodic-acid-Schiff stains (eumycetoma).
The study of discharged granules crushed on the slide and stained with lactophenol blue particularly allows differentiation between the thin filaments of actinomycetoma and the thicker hyphae of eumycetoma. Hence, these special stains are of value in further confirming the the nature of the organism.

Histology:

Histological sections stained with H & E stain show suppurative granulomas (composed of neutrophills), surrounding characteristic grains in the subcutaneous tissue. Neutrophillic infiltrate is surrounded by palisading histiocytes beyond which a mixed inflammatory infiltrate comprising of lymphocytes, plasma cells, eosinophills, macrophages and fibrosis was seen with multinucleated gaint cells.
In case of Actinomycotic mycetoma, the actinomycetoma grain is surrounded by homogenous eosinophillic material (Splendore-Hoeppli reaction). In cases of eumycotic mycetoma, thick club-shaped structures (chlamydospores) are seen.

Culture:

Grains of many species have overlapping morphological features and therefore culture is required for an accurate identification of the causative agent. Clinical specimens should be inoculated into primary isolation media, like Sabouraud's dextrose agar.

Serology:

Serolological tests are not available routinely. However, they are gaining importance as highly usefull diagnostic procedures in the early stages of the disease, before the granules are formed. ELISA appears to be a sensitive test for the detection of antibodies in mycetoma infections, especially in epidemiological work [12].

Advanced diagnostic techniques:

Modern molecular techniques have been developed, including rapid and inexpensive species-specific PCR analysis, which have permitted identification of new species and phylogenetic relationships [13-15].

Imaging techniques

Radiology and ultrasonography enable assessment of disease extent and bony involvement if any [16]. The use of helical computed tomography has recently been shown to provide detailed assessments of soft tissue and visceral involvement [17]. Magnetic resonance imaging (MRI) provides the most comprehensive method for assessment of the bone and soft tissue involvement and may also be useful in evaluating the differential diagnosis of the swelling [18,19].

Treatment

The choice of treatment for mycetoma depends on the causative organism which has been identified on the basis of morphology of grain in histopathology sections.
Actinomycetomas are usually amenable to antibiotic treatment. In the treatment of actinomycotic mycetoma, sulphonamides, rifampicin, tetracyclines, isoniazid, streptomycin, amikacin and amoxicillin-clavulanic acid have been used with variable results [20-22]. The addition of aminoglycosides and cotrimoxazole gives higher efficacy, and is associated with shorter treatment duration. Parenteral amikacin and oral cotrimoxazole combination is especially advocated for use in cases at risk of pulmonary spread or vertebral involvement [21,22]. Cure rates vary widely, ranging from 60% to 90%. Combined treatment is preferred to prevent the development of drug resistance and to eradicate any residual infection [23].
Eumycotic mycetomas usually respond less well to drug therapy and are therefore managed by long courses of antifungals, combined with aggressive surgical excision or debulking of the lesions. Thus complete surgical excision of the lesion and post surgical medical therapy should form the first line of management in eumycotic mycetoma. Griseofulvin, amphotericin and terbinafine have shown a limited or poor response [24,25]. Fluconazole has not been found to be effective but ketoconazole and itraconazole have both been shown to have a good efficacy [26,27]. Itraconazole and terbinafine are presently the major antifungal agents considered for the medical management of eumycetoma [28]. Newer broad-spectrum triazoles, such as Voriconazole and Posaconazole have been reported to have promising results for patients of eumycetoma which is refractory to standard therapies [29,30]. However their high costs are prohibitive for use in moost endemic regions.

Conclusion

Since mycetoma is a relatively painless condition, it is often diagnosed at an advanced stage. There is a high incidence of secondary bacterial infection in mycetoma lesions. This can cause increased pain and disability as well as septicemia which may be fatal if untreated. This emphasizes the need for its correct diagnosis after meticulous clinical examination, assisted by histological and microbiological studies along with the use of special stains and a proper treatment.

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