REVIEW ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Mycetoma of the Head and Neck: A Re-appraisal

Anuradha Sharma[1], Neelam Singh[2], Nupur Gupta[1]*, Tanya Thakkar[3], Shaiza Khan[3]

Abstract

A neglected tropical disease, declared by the WHO in 2016, mycetoma, is a chronic granulomatous, mutilating and debilitating disease. Apart from affecting the lower limbs, it also affects the cervico-facial region, chest and abdomen. In the cervico-facial region, mycetoma of the paranasal sinuses, scalp, ear, and tongue have atypical presentation. Sinus mycetoma can be sequelae to allergic fungal sinusitis due to the raised intracranial pressure effects of mycotoxins whereas mycetoma of the scalp may present without discharging granules. Neglect of fungal sinusitis, chronic pain in the scalp can be detrimental in the long run. In the oral cavity, minor trauma and bad oral hygiene can contribute to mycetoma of the tongue or oral cavity, the latter being rare. Dental surgeons can also help in the early detection of mycetoma of the oral cavity and para-nasal sinuses, during dental examination. This article aims to review mycetoma of the cervico-facial region with the objective of addressing ways for early diagnosis.

Keywords: *Actinomadura pelletieri,* Dentists, Diagnosis, Early, Eumycetoma, Face, Fungi, Immunity, *Madurella mycetomatis*, Oral hygiene, Skin, Subcutaneous tissue, Quality of life

Asian Pac. J. Health Sci., (2022); DOI: 10.21276/apjhs.2022.9.2.16

Introduction

Mycetoma is one of the neglected tropical diseases, characterized by massive deformity, disability and can be fatal if not managed properly and timely. It is a mutilating, chronic, granulomatous infection of the subcutaneous tissue, muscles and bone mainly caused by bacteria and fungi which are found in soil and water. The disease primarily affects the foot and rarely other parts of the body. Although it is a preventable disease in early stages, it has high morbidity and enormous socio-economic implications. Epidemiologically, mycetoma is prevalent in almost all parts of the world and is most commonly found in countries in the "Mycetoma belt" that include Sudan, Somalia, Senegal, Yemen, Venezuela, Mexico, some parts of Pakistan, and India.[1,2]

Clinically, the lesion is presented by swelling, sinus tracts and production of granules in the affected body part. The grains may differ in color, size and consistency depending on the causative agent.[2]

The rural and poor populations in remote areas are most exposed to the infection, due to a lack of trained staff, health facilities, diagnostic tools, and treatment. Other factors that may influence the treatment are the chronic course of the disease and poor treatment outcome in eumycetoma.[3] The treatment modality in mycetoma infections is primarily surgical in the case of fungal mycetoma and therapeutic in the case of actinomycotic mycetomas.

Historical Timelines

Description

The oldest description of this disease dates back to the ancient Indian Sanskrit text Atharva Veda, in which reference is made to *Pada Valmikam*, meaning "anthill foot." In 1842, Dr. John Gill first recognized mycetoma as a disease entity in the southern province of Madura, India, while working at a dispensary. Colebrook in 1848, along with Gill provided a clear description of the disease as part of their *Madura Dispensary Reports*. Godfrey was the first who documented a case of mycetoma in Madras, India. However, the term "Mycetoma," meaning fungal tumor, was proposed by Vandyke Carter in 1860, who established its fungal etiology. This terminology was published by Colebrook.

[1]Department of Microbiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India.

[2]Department of Conservative Dentistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India.

[3]Department of Intern, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India.

Corresponding Author: Nupur Gupta, Department of Microbiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India. Mobile: 9810616434. E-mail: ngupta4@jmi.ac.in

How to cite this article: Sharma A, Singh N, Gupta N, Thakkar T, Khan S. Mycetoma of the Head and Neck: A Re-appraisal. Asian Pac. J. Health Sci., 2022;9(2):72-79.

Source of support: Nil

Conflicts of interest: None

Received: 17/11/2021 **Revised:** 09/12/2021 **Accepted:** 22/01/2022

Classification

In 1872, Colebrook classified the disease into melanoid (black) and ochroid (pale) based on the color of the grains produced by the etiologic agents. Later, Pinoy recognized the possibility of classifying the cases of mycetoma by grouping the causative organisms, and the formal classification was put into place by Chalmers and Archibald, who divided them into two groups, Group1, Maduramycosis caused by true fungi, and Group 2, Actinomycosis, caused by actinomyces, the higher bacteria.[4]

National Capacities on Mycetoma

The First International Training Workshop on Mycetoma was convened in Khartoum on 10th–14th February 2019 by the Government of Sudan and WHO to build national capacities on mycetoma. The expertise of the Mycetoma Research Centre

in Khartoum shared their experiences and elaborated on the standardization of practices relating to diagnosis, treatment, and surveillance of mycetoma. This was followed by the Sixth International Conference on Mycetoma in Khartoum from 15th to 17th February 2019. It was here that the "Khartoum Call for Action on Mycetoma" was adopted to take specific public health and policy measures to address the burden of mycetoma.[5]

Review of Literature

1. In 1997, Klossek *et al*. reported 109 cases of mycetoma of paranasal sinuses. Clinical presentation varied from pan-sinusal involvement to a simple mycetoma hanging in a superior meatus, non-invasive in nature. Diagnostic tools such as nasal endoscopy and computed tomography (CT) were used. Heterogeneous sinus opacity with micro-calcifications as well as homogeneous opacity with bone lysis was suggestive of mycetoma. Surgical debridement was done using functional endoscopic sinus surgery. The advantage was that a wide opening of the affected sinuses could be done with careful extraction of all fungal material. No post-operative therapy was given and only four recurrences were seen.[6]
2. In 1997, De Shazo *et al*. reported sinus mycetoma in five patients who had a history of frequent atopy, and nasal polyps. One patient had both allergic fungal sinusitis and a mycetoma in the same sinus. Only one patient had a history of exposure to fungus during continuous positive airway pressure with in-line humidification for obstructive sleep apnea, several months before the onset of symptoms. The apparatus used to be cleaned intermittently and black, "sticky" material in the tubing and nebulizer reservoir had been noted sometimes. Two patients were first found to have mycetoma as part of an evaluation for new onset adult epilepsy. The release of fungal proteins or intracranial pressure effects may have played a role in the induction of the mycetoma. Neurologic complications such as optic neuritis and ophthalmoplegia have been postulated to have been caused by mycotoxins. Immediate hypersensitivity skin test response to 60 commercially available fungal, other inhalants and environmental antigens was seen in all the five patients. Histopathology of the sinus mucosa showed chronic inflammatory cells infiltrate with extramucosal accumulations of tangled hyphe in various stages of decay in four patients. The sinus mucosa of the third patient showed patchy, dense inflammatory infiltrate of lymphocytes, plasma cells and many eosinophils and rare hyphal elements were visible on Periodic acid-Schiff and Gomori methenamine silver staining. Calcification within the sinus was seen on CT. Response to surgical treatment was seen in all the cases. The case finding criteria was modified into proposed diagnostic criteria for sinus mycetoma and included the following: exclusion of patients with invasive fungal sinusitis and differentiation of sinus mycetoma from other forms of non-invasive fungal sinusitis on the basis of specific histopathologic findings. Accordingly, sinus mycetoma represented a distinct but not necessarily isolated element in the spectrum of non-invasive fungal disease of the sinuses.[7]
3. In 2003, Jacobsen and Casagrande observed that pain in the teeth can be a manifestation of an underlying problem of sinusitis.[8]
4. In 2004, Matjaz *et al*., reported at the Clinic of Otorhinolaryngology and Cervicofacial Surgery in Ljubljana, fungal mycetoma in a lady aged 22 years. She had come with swelling and periodic pain in left cheek region. She had received treatment for left maxillary first molar for 1 year revealed. An opaque foreign body was seen at the bottom of the left maxillary sinus in the X-ray of the paranasal sinuses. Endoscopic sinus trepanation was done and the foreign body was removed. It was sent for histolopathological examination which showed the presence of fungal hyphe and mycological analysis confirmed *Aspergillus fumigatus*. There were no untoward events after the operation, and she had no evidence of the disease at 4 months follow-up.[9]
5. In 2008, Palacios *et al*., reported in New Orleans, mycetoma of the sinonasal area in a male aged 31 years. There was colonization of the sino-nasal cavity by fungal hyphe. There was a history of fungal sinusitis 4 years earlier that had been successfully treated with surgery. Some patients with mycetoma may complain of chronic sinusitis, while others are asymptomatic. More common in women than in men, the most frequently involved sinus is the maxillary sinus and is often seen in immunocompetent persons with no deficiency of IgA, IgM or IgG.[1]
6. In 2010, Fahal and Sabaa, reported in Sudan, mycetoma lesions on different parts of the body in seven hundred and twenty two children during the time period May 1991 to March 2009. Five thirty one were male and 191 were females within an age range of 14–17 years. Most of the children had eumycetoma. The foot was the most affected part followed by the knee, hand, head and neck, chest wall and buttocks. Diagnosis was based on surgical biopsies, ultrasonic examination, cytology and histopathological examination. All patients were treated medically according to the type of mycetoma. Some children needed surgical treatment also.[10]
7. In 2011, Diallo *et al*., reported in Senegal, an unusual presentation of mycetoma of the scalp. Since 2 years, a lady from the rural area of Senegal had been suffering from pain in the scalp.

On examination, two soft tumid lesions, three cm in diameter, with crusty surface were seen on the vertex. There were no granules and no abnormalities in the X-ray of the skull. Polymorphous granulomatous infiltrate with foci of suppuration circumscribing small, irregular grains with radiating filaments was seen in skin biopsy. *Actinomadurella pelletiere* was cultured on Lowenstein Jensen medium. Cotrimoxazole therapy for 8 months was helpful in treating the lesions.[11]

8. In 2011, Welsh *et al*. in Mexico, reported in a 44 year woman, mycetoma of the scalp and eye. The lesion was red, friable, granular and vascular. The etiological agent was identified as *Nocardia brasiliensis*. It was cured in 12 weeks with a combination therapy of amikacin and sulphamethoxazole.[12]
9. In 2013, Zuniga *et al*. in Spain, reported in a 79-year-old rural worker, hard tumified lesion on the right side of the scalp. There was history of trauma due to wood branch 9 months before. The discharge was sero-sanguinous in nature containing white granules. There was no bone involvement in CT and Magnetic resonance imaging (MRI). The causative organism was identified as *N. brasiliensis*. The patient responded to monotherapy by trimethoprim-sulfamethoxazole.[13]
10. In 2015, Arora and Handa reported in Bahrain, in a first of its kind, an unusual case of actinomycetoma of the temporal

bone. The presenting symptom was discharge from the ear. Biopsy from the granulations showed dense, acute or chronic inflammatory tissue reaction with osteo-invasion. Histopathological studies showed suppurative granuloma with Splendore–Hoeppli phenomenon. Microscopic examination showed pus cells and culture showed growth of *Nocardia asteroides* suggestive of actinomycetoma. Treatment was done with a combination of intravenous gentamicin 1.5 mg/kg twice daily and tablet cotrimoxazole 320-trimethoprim/1600 sulfamethoxazole (DS) mg twice daily orally for 5 weeks in the initial intensive phase. The maintenance phase of treatment was done with oral cotrimoxazole DS once daily and rifampicin 600 mg once daily for 2 months.[14]

11. In 2015, Fahal *et al*. in Sudan, conducted a descriptive, cross-sectional study on 49 patients with mycetoma of head and neck at the Mycetoma Research Centre, University of Khartoum, Sudan between 1991 to 2014. The different investigations carried out were fine needle aspiration, histopathological examination of biopsies and imaging techniques of the affected sites. Results of the study showed inclusion of frontal region in twelve patients, occipital in five patients and temporal in one patient. Multiple skull bones were also involved. There was involvement of orbit, upper eyelid, buccal cavity and cheeks.[15]
12. In 2018, Ahmed *et al*. described a male patient aged 13 years, who was diagnosed with fungal mycetoma of the cervico-facial region. There was ulcer tumefaction at the cervico-facial region. Examination showed inflammatory swelling under and around the hyoid, extending to the left mandible and parotid region. Naso-fibroscopy showed edema of arytenoids and ventricular bands and laryngeal hypomobility. Cervical and laryngeal biopsies were also done. Histological findings showed black grains associated with the discharge. Considering the depth of the lesion terbinafine was started as a line of treatment.[16]
13. In 2019, Torul *et al*., reported in Ordu University Institute of Health Sciences, Turkey, maxillary sinus aspergilloma after tooth extraction, in a lady aged 40 years. She had presented to the clinic for temporomandibular joint problems. There was no remarkable sign on clinical examination. A radio-opaque foreign body was noted in the right maxillary sinus, in the panoramic radiography and its exact location was done by Cone Beam CT. There was no bony destruction. The foreign body was removed with the Caldwell-Luc procedure under local anesthesia. The histopathologic examination of the specimen revealed the presence of hyaline septate fungal hyphe with acute angle branching resembling Aspergillus spp. She was started on antibiotics, analgesic, mouthwash, and decongestants drugs. Follow-up at 6 months showed no evidence of the disease.[17]
14. In 2020, Al-Rawee and Saeed reported a case of actinomycosis of the tongue in a lady aged 65 years. Since 1 year, she had a small mass in the tongue. Examination revealed a painless, boil-like lesion in the anterior third of tongue, located submucosally. Benign neoplasm was considered as a part of diagnosis and a surgical biopsy was done. Augmentin 625 mg twice a day and paracetamol 500 mg on need was prescribed for 7 days. Mycetoma of the tongue was made on histopathological basis. Patient was advised tetracycline capsule 250 mg for 1 month.[18]
15. In 2021, Nazari *et al*. reported a case of fungal septal abscess with maxillary sinus mycetoma in an immunocompromised lady aged 32 years. She reported with facial pain and nasal obstruction since 4 days. There was no history of fever, history of dental treatment or head ache. On examination, the anterior part of the nasal septum showed swelling bilaterally. Nasal endoscopy showed mucopurulent discharge in the left middle meatus.

A complete blood profile and CT of paranasal sinuses was done. Incision and drainage of the septal abscess by left meatal antrostomy was done. Histopathological examination showed fungal hyphe. Intravenous antibiotic treatment was given for 1 week. Possible cause of the disease was from direct sub-periosteal extension from the sphenoid bone or through bony fissure or thrombophlebitis.[19]

Epidemiology

Geographical Distribution

Mycetoma has a worldwide, albeit uneven distribution. The disease is endemic in tropical and subtropical regions and the African continent has the highest prevalence. In Africa, mycetoma is most frequently seen in Sudan, Senegal, Mauritania, Kenya, Niger, Nigeria, Ethiopia, Chad, Cameroon, Djibouti and Somalia. They are also seen in temperate regions.[1]

Age Distribution

The condition is most common in young adults in the age group of 25–50 years. It is uncommon in children.

Gender Distribution

Mycetoma is more commonly reported in males than females in a ratio of 3:1. This is probably because men are more commonly involved in agricultural work. It has been also hypothesized that the female hormone progesterone and estrogen might be having some repressive effect on the growth of micro-organisms.[20]

Environmental

Overall, most cases of mycetoma occur in arid and hot climates, having a short period of heavy rainfall with milder temperatures. Actinomycetoma is more prevalent in drier areas, whereas eumycetoma is more common in sites with more rainfall and having savannahs or forests with thorny trees and scrubs.[4,21]

Eumycetoma prevails in the mycetoma belt that stretches between the latitudes of 15° South and 30° North. The belt includes Sudan, Somalia, Senegal, India, Yemen, México, Venezuela, Columbia, Argentina and other countries. Around 75% of mycetomas are actinomycotic in certain parts of India. However, eumycotic mycetoma accounts for the majority of cases reported from the Northern region.

Etiological Agents

The most prevalent causative agent of eumycetoma worldwide and in Africa in particular, is *Madurella mycetomatis*. In some parts of central Africa, including Sudan, *M mycetomatis*

causes more than 70% of all mycetoma infections. The white grain eumycetoma itself is very rare as compared to black grain eumycetoma and actinomycetoma. In Mexico, 98% of the mycetoma are the aerobic actionomycetales, mainly *N. brasiliensis* and *Actinomadura madurae.* In India, 65% of mycetoma are caused by aerobic Actinomycetales and *M. mycetomatis.* In the United States, most of the mycetoma cases are due to filamentous fungi identified as *Pseudallescheria boydii* or *Exophiala jeanselmei*.[2,21,22]

Pathogenesis

Microbial Etiology

The organisms causing mycetoma can be classified into bacterial and fungal. The bacterial causes of mycetoma are the actinomycotic species such as *Streptomyces somaliensis*, *A. madurae*, *N. brasiliensis*, and *N. asteroides.* The fungal causes of mycetoma are classified based on the color of the grains into white grain and black grain eumycetoma. The white grain mycetoma is caused by various species of genus *Acremonium*, *Pseudallescheria*, *Aspergillus*, *Fusarium*, and *Scedosporium.* The black grain eumycetoma is caused by *M. mycetomatis*, *Madurella grisea*, *E. jeanselmei*, *P. boydii*, *Leptosphaeria senegalensis*, and *Curvularia geniculata* species. Depending on the etiology, the disease is classified into two types, actinomycetoma and eumycetoma.[23-25] Both the diseases can be distinguished on the basis of a few clinical differences as shown in the following table:

Sites of Infection

The most favorable site of infection is usually the foot in 70% of patients followed by the hand in 12% of patients. Less common sites reported are the arm, leg, thigh, back, gluteal region head and neck, thorax, scalp, and knee. Oral mycetoma is rare. Mycetoma of the head, neck and jaw cavity can be fatal, leading to death because it can spread into adjoining vital organs.[9,22]

Route of Infection

The route of infection of mycetoma is always exogenous with the micro-organism getting access through trauma. Trauma is usually due to thorn, grasses, wisp of straw and hay, wood spicule, plant fiber, nail, or needle. In the oral cavity, the route of infection can be through endodontic intervention on the teeth of the maxilla, which are in contact with the sinus, or after insertion of dental implants in this area. Some factors contribute as predisposing factors such as operated wound, wide open injuries, scratches and friction in minor surface injuries.[9,22]

Predisposing Factors

Multiple factors contribute as predisposing factors to the formation of mycetoma. These are denoted as follows:

Environmental

Climate related

Mycetoma cases are mainly seen in hot and dry climates with intermittent short periods of heat and rainfall. The pathogens causing mycetoma are present in the soil and usually enter the human body through a thorn prick or similar kind of trauma.

Micro-environment of the body

Chronic sinusitis or changes in the naso-sinosal micro-environment after surgery or radiotherapy are some of the factors leading to mycetoma of the paranasal sinuses.[1]

Anatomy

The nose corridors are anatomically quite tortuous. The normal ventilation of the nose and drainage of the jaw cavity is compromised due to deviations, cristae and spinae of the nose column, pneumatized middle nose conch and other abnormalities in the middle nose corridor. The accumulated mucus thereby provides a rich base for the growth of *Aspergillus* spp.[9]

Host factors (immunological and genetic)

Host genetic factors may regulate susceptibility to mycetoma and other fungal infections. There are complex genetic traits in which multiple genesinteract with each other, environmental factors, as well as the microbe, to cause disease. A total of thirteen genes with allelic variants are found to be associated with mycetoma. These genes lie in different pathways and systems such as innate and adaptive immune systems, sex hormone biosynthesis, and some genes coding for host enzymes.[19]

Clinical Presentation

Mycetoma can remain for more than 10 years at the site of infection. It should be diagnosed at the initial stage only and appropriate therapy should be started, before the lesions go into the advanced stage.

Initial stage

In initial stages, the lesion develops as a hard, painless, subcutaneous lump. After a few months, caves can be seen in the center of the lesion which ulcerate and discharge pus with grains. Sinus tracts develop, discharging the grains to the skin surface. The skin surface looks scarred and pale. There is no pain but the surface may itch or burn. In a jaw cavity mycetoma, there is periodic malodorous ulcerous discharge from the nose.[9]

Advanced stage

As the disease advances, there is development of deformity, due to spread of the infection through fascial planes. This impinges on and knocks down the muscles, fascia and bones of the adjacent area. The affected site is grossly swollen with club shaped masses

S. No.	*Features*	*Actinomycetoma*	*Eumycetoma*
1.	Clinical representation	Less well defined lesion	Lesion is firm and round, soft and lobular.
2.	Course of infection	More rapid	Progression is slow
3.	Bone involvement	More extensive	Less extensive
4.	Grain color	Different color but not black	Black / white

of cystic areas, interconnected sinus tracts and fistulae, discharging exudates containing grains to the skin surface. Secondary bacterial infection is common and represented by tenderness in affected areas. Extensive muscle and bone destruction involvement causes incapacitation. The wasting and anemia can also be seen in mycetomatous infection because of the loss of livelihood from incapacitation.

Lymphatic and Hematologic Dissemination

Most of the patients are devoid of regional lymph node enlargement. An enlarged lymph node signifies secondary bacterial infection although actual lymphatic spread may also occur in mycetoma. Metastatic lesions at distant lymph node are also reported in actinomycetoma. Hematological spread is rare. Multiple inadequate surgeries are considered to be the cause of lymphatic spread.[20]

Diagnosis

The diagnosis of mycetoma is based on clinical examination along with laboratory identification of the causative organism.

Clinical Diagnosis

The clinical triad of a subcutaneous mass, sinuses and granular discharge, seen in patients from an endemic area are typical diagnostic features for mycetoma.

Laboratory Diagnosis

Multiple diagnostic tools can be used to identify the causative agents of mycetoma in the discharge which is collected from the sinuses and/or the biopsy from the lesions. These are:

1. Gross observation of the grains present in the discharge.
2. Microscopic examination and microbiological culture of the grains.
3. Histopathological examination of the biopsy.
4. Radiology imaging techniques.
5. Phenotypic characterization and molecular diagnostics.

The definitive procedures for establishing the diagnosis of mycetoma are direct examination with 10% potassium hydroxide (KOH), microbiological cultures and biopsy.[23,26,27]

Microscopic examination and culture are performed on the discharge from the draining sinuses obtained by FNAC or tissue biopsy of the affected site. The samples are cultured on Sabouraud's dextrose agar and blood agar to isolate fungi and bacteria. The etiologic agents are identified according to their macroscopic and microscopic features.[28]

Histopathological specimen obtained by deep biopsy is examined with hematoxylin and eosin stain and have been used as the sole identification method in many centers. An initial neutrophilic response occurs in response to bacterial invasion which later results in the formation of a granuloma. Practical limitations make identification up to the species level challenging, because of their similar appearance.[29,30]

Radiology helps in clinical diagnosis especially in the follow-up of disease progression, development of a surgical strategy and assessing the clinical cure. MRI helps in the differential diagnosis and assessment of the degree of bone and soft tissue involvement. Mycetoma, skin, muscle, and bone grading system is used to describe and grade disease severity on the basis of MRI findings. The dot-in-circle sign in MRI is an easily recognizable and a specific sign of mycetoma. Panoramic radiographic examination and Cone Beam CT are necessary diagnostic procedures in the scenario of odontogenic mycetoma of the maxillary sinus.[3,9,31,32]

Ultrasound clearly discriminates mycetoma from other subcutaneous masses and is the preferred imaging technique to accurately define the extent of the lesion which can be useful for planning surgical procedures. Sharp hyper-reflective echoes are caused by the grain's cement substance. In eumycetoma, cavities can be seen with or without acoustic enhancement. In actinomycetoma, the grains are smaller in size with individual embedding and absence of cement and are less distinct.[33]

Diagnostic difference between eumycetoma and actinomycetoma are denoted in the following table:[25]

S. No.	*Features*	*Eumycetoma*	*Actinomycetoma*
1.	Organism involved	Fungi	Bacteria
2.	Rapidity of the lesion	Slowly progressive	Rapidly Progressive
3.	Affected body parts	Most commonly foot	Most commonly foot but other parts involvement is also there
4.	Discharging sinuses	Few	Many
5.	Color of grains	White or black	Different color
6.	Bone invasion	May or may not be there•	Rapid
7.	Radiograph features of cavities	• Cavities are smaller in number. • Large size cavities are present. • Margins around the cavities are clear.	• Numerous • Small size cavities are present. • Margins around the cavities remain unclear.
8	Ultrasonographic picture	Thick walled cavities with hyper-reflective echoes are seen.	Fine Echoes are seen.
9	10% Potassium hydroxide mount of grains.	Presence of fungal hyphe is noted.	Structures resembling fungal hyphe are not seen.
10	Staining techniques	Gram stain, Periodic-acid-Schiff, Gomori methanamine silver.	Gram stain, Modified Zeihl Neelson stain.
11	Molecular diagnosis	Pan-fungal PCR	16s RNA gene sequencing studies.
12	Treatment	Partial cure or improvement	Improvement in most cases.

Clinical and Experimental Dermatology.2019; 44: pg126.

Differential Diagnosis

It is necessary to rule out other lesions or diseases resembling mycetoma, because the entire treatment is dependent on that. These conditions include, botryomycosis (causative agent is *Staphylococcus aureus*), coccidiomycosis, osteomyelitis, syphilis, tuberculosis, leprosy, chromoblastomycosis, other deep mycosis and bone and soft tissue tumors.

Treatment

Treatment and management of both the groups of mycetoma requires different regimes. Hence, correct identification is an essential requirement. Eumycetoma requires adequate antifungal therapy and surgery and is more difficult to treat. Surgical treatment is indicated for small, localized lesions and also for large lesions to reduce the organism load.[34,35]

Treatment of Actinomycetoma

Actinomycetoma responds to a combination of antimicrobial agents. In 1940's and 1950's, the combination of choice was streptomycin sulfate and diamino diphenyl sulfone. In case of no response, combination of streptomycin and trimethoprim-sulfamethoxazole was given and treatment duration ranged between 6 months and 4 years with a mean of 18 months. Nocardial actinomycetoma responds to sulfonamides with reported cure rates up to 90%, with a mean duration of therapy of 1 year or more. More recently trimethoprim-sulfamethoxazole at a dose of 8/40mg/kg/day for 5 weeks and amikacin at 15 mg/kg/day in a divided dose every 12 h for 3 weeks has been recommended in the form of five to ten cycles. Amikacin can be replaced by netilmicin. The renal and audiometric functions are monitored closely during the entire treatment tenure.[29,36]

A two-step schedule was proposed by Welsh for the treatment of actinomycotic mycetomas. In the initial intensive phase of 5–7 weeks, four injections of penicillin and two of gentamicin was given daily, followed by a maintenance phase of amoxicillin/doxycycline and cotrimoxazole till 2–5 months after complete healing. A modified two-step treatment for actinomycetoma consists of an intensive phase of intravenous gentamicin with oral cotrimoxazole twice daily for a period of 4 weeks, followed by the maintenance phase of cotrimoxazole and doxycycline given twice daily for 5–6 months. Other drugs are also tried in combination with co-trimoxazole such as dapsone, netilmicin, and linezolid 600 mg twice a day, orally. Oral use of drugs reduces the expenses of hospitalization. In patients allergic to co-trimoxazole and non-responders to therapy, amoxicillin-clavulanate or carbapenems can be prescribed. In pregnant patients, amoxicillin clavulanate is considered to be the safest drug.[37]

Treatment of Eumycetoma

The treatment of eumycetoma is challenging due to extended periods of antifungals along with surgical management, such as wide local excision, debridement and amputation. Recurrence is common due to non-compliance, an absence of response or inadequate response to antifungal therapy and surgery. Of all antifungal drugs available at present, only the drugs belonging to the azole class have sufficient *in vitro* sensitivity against *M. mycetomatis*. Ketoconazole at a dose of 400–800 mg/day for 9–12 months has been the mainstay of treatment for decades since the 1980s. It was recommended in 1984 by Mahgoub and Gumaa. Its high toxicity and side effects led to it being replaced by itraconazole, a less toxic drug, at a dosage of 200–400 mg/day for 6 months to 3 years.[38]

Treatment of Jaw Cavity Mycetoma

Endoscopic surgery through the nose corridor along with trepanation of the front wall of the jaw cavity is done to remove the fungal lesion in entirety. This need not be supplemented with antimycotics postsurgery.

Recent Update

There are possibilities of developing preventive and personalized strategies in the future, based on next-generation sequencing studies. These will help to find out the genome for variants associated with mycetoma. Potential target pathways can be identified for new treatments for mycetoma and at-risk individuals can be identified.[24]

The glycolytic enzyme fructose-bisphosphate aldolase which is expressed on the hyphe present in the mycetoma grain might be useful as a candidate antigen for a future vaccine against mycetoma.[39]

Prevention

Till date, there is no vaccine for mycetoma, so people should be educated and made aware about activities to be avoided that would otherwise expose them to agents of mycetoma. One should refrain from carrying sticks and thorny branches that have had contact with soil, especially if contaminated with cattle dung. In dusty areas, face and head should be covered so as to avoid exposure. Persons with atopy should be careful and avoid exposure to fungal agents. Use of nebulisers by patients should be done with caution with regular cleaning and drying. Use of continuous positive airway pressure with in-line humidification for obstructive sleep apnea should be done with great caution with an alert eye on any black spots appearing in the lines. All humidifiers should be cleaned and changed frequently.

Dental Clinic and Mycetoma

Usually, foot is the favorable site for mycetoma to develop, but other body part involvement can also be there. Fungal mycetoma of head and neck region is rare and remain asymptomatic in initial stages. The diagnosis is frequently made when the lesions are extensive.

Iatrogenic Cause of Mycetoma

A few studies have shown dental cause in developing lesions of head and neck. Most common sites are the temporal region, cervical region and maxillary sinus. Some materials used in dental practice to treat pulp diseases exhibit substances that allow fungal growth, leading to mycetoma formation. These materials usually come in the pastes used for root canal obturation. Root canal filling materials contain oxides of zinc, bismuth, barium, sulfur, titanium and lead, salts of calcium and some organic components. These materials are favorable for the growth of fungi.[9]

Tooth extraction has also been a cause for orofacial mycetoma. Torul *et al*. reported a case of maxillary aspergilloma with a precious history of tooth extraction. They suspected spread of infection

from the tooth socket into the maxillary sinus and subsequent aspergillus infection in the sinus. Other dental treatments such as periodontal therapy, dental implants, alveolar grafting have known to cause sinus aspergilloma.[18]

In Early Diagnosis of Sino-nsasl Mycetoma

In sino-nasal mycetoma, the congestion and pressure is referred to the tooth. This is because the roots of the upper teeth and jawbone are in proximity to the sinuses. Here, the dental surgeon can differentiate sinusitis from odontogenic pain and initiate appropriate treatment quickly.[8]

Therefore, when searching for causes of fungal inflammation in the jaw, it should be taken into consideration that the possibility of favorable conditions for the fungal growth also originate in non-treated periapical changes in maxillary teeth, and in interventions in which dental materials penetrate into the jaw cavity.[9]

Conclusion

Mycetoma of the head and neck region poses a serious medical and health problem and is associated with serious complications. The initial presentation can be variable, delaying the institution of a proper treatment. Early diagnosis is critical for treatment, reducing the associated morbidity with this condition. Culture along with histopathological examination should be done in all facilities. In remote areas, this might be a challenge in diagnosis, so better laboratory facilities with trained staff should be posted in such areas. The expensive and frequently unsatisfactory nature of the treatment, low cure rate and high follow-up dropout rate makes the treatment more challenging. Many side effects and non-availability of medicines in endemic areas makes this disease a challenge to deal with. This can be addressed through government health policies and extensive drug delivery systems. The route of infection, susceptibility and resistance in mycetoma is poorly understood and this is compounded by the lack of preventive and control measures. Education of the masses, especially in the rural areas is long-awaited. They have to be made to understand the routes of infection of this disease, through flow diagnosis in the local language, in a pictorial and colorful form. Along With this, they should be cajoled by the local health officers to spread any trauma to the head and neck region in weekly health meetings. The severe physical disabilities and social stigma associated with this disease leads to isolation and further delay in treatment and consequent complications. Dental surgeons can play a major role in capturing the early signs and symptoms and referring the patients pre-emptively to a concerned physician or surgeon. Health education along with timely intervention by dentists, ear-nose-throat surgeons can reduce disease morbidity and mortality.

Highlight

This manuscript has highlighted the fact that mycetoma of the head and neck can have an insidious onset and can be arrested early by intervention of local health authorities as well as dental surgeons.

Acknowledgment

It is hereby acknowledged that all the authors have contributed substantially in the making of this manuscript. Dr. Anuradha Sharma for concept, design and final review; Dr. Neelam Singh and Dr. Nupur Gupta for critical analysis and scientific inputs; Ms. Tanya Thakkar for literature search from online databases and Ms. Shaiza Khan for editing the final manuscript.

The manuscript has been read and approved by all the authors, the requirements for authorship have been met and each author believes that the manuscript represents honest work

References

1. Palacios E, Jones W, Alvernia J. Sinonasal mycetoma. Ear Nose Throat J 2008;87:606-8.
2. Wankhade V, Sawatkar G, Supekar B, Pratap R, Bhat D, Tankhiwale S. Mycetoma: A common yet unrecognized health burden in central India. Indian Dermatol Online J 2019;10:256.
3. El Shamy M, Fahal A, Shakir M, Homeida M. New MRI grading system for the diagnosis and management of mycetoma. Trans R Soc 2012;106:738-42.
4. Agarwal P, Relhan V, Mahajan K, Garg V. Mycetoma: An update. Indian J Dermatol 2017;62:332.
5. Mahgoub E. Mycetoma. In: Tropical Infectious Diseases, Principles, Pathogens, and Practice. 2nd ed., Vol. 2., Ch. 78. Amsterdam, Netherlands: Elsevier; c2006. p. 892-7.
6. Klossek J, Serrano E, Péloquin L, Percodani J, Fontanel J, Pessey J. Functional endoscopic sinus surgery and 109 mycetomas of paranasal sinuses. Laryngoscope 1997;107:112-7.
7. DeShazo R, O'Brien M, Chapkin K, Sotoaguilar M, Swain R, Lyons M, *et al*. Criteria for the diagnosis of sinus mycetoma. J Allergy Clin Immunol 1997;99:475-85.
8. Jacobsen PL, Casagrande AM. Sinusitis as a source of dental pain. Dent Today 2003;22:110-3.
9. Matjaz R, Jernej P, Mirela KR. Sinus maxillaris mycetoma of odontogenic origin: Case report. Braz Dent J 2004;15:248-50.
10. Fahal AH, Sabaa AH. Mycetoma in children in Sudan. Trans R Soc Trop Med Hyg 2010;104:117-21.
11. Diallo M, Niang SO, Tounkara T, Fricker A, Mbaye PS. Unusual presentation of mycetoma caused by *Actinomadura pelletieri* on the scalp. Med Trop (Mars) 2011;71:179-80.
12. Welsh O, Morales-Toquero A, Cabrera-Vera L, Vazquez-Martinez O, Gómez-Flores M, Ocampo-Candiani J. Actinomycetoma of the scalp after a car accident. Int J Dermatol 2011;50:854-7.
13. Zúñiga M, Hunziker M, Nico M, Rivitti E, Festa-Neto C. Actinomycetoma of the scalp due to *Nocardia brasiliensis*: Case report and review of the literature. Int J Dermatol 2013;54:695-8.
14. Arora V, Handa B. Actinomycetoma of temporal bone: A rare case report. Indian J Otol 2015;21:298.
15. Fahal A, Mahgoub ES, El Hassan AM, El Rahman AM. Mycetoma in the Sudan: An update from mycetoma research centre, university of Khartoum, Sudan. PLoS Negl Trop Dis 2015;9:e0003679.
16. Ahmed H, Ndiaye C, Mbaye A, Pilor ND, Dieye A, Ndiaye IC. Cervical mycetoma: An infectious disease that behaves like cancer. J Otolryngol ENT Res 2018;10:406-8.
17. Torul D, Sunar C, Erdem H. Isolated maxillary sinus aspergilloma associated with tooth extraction: Case report short title: Fungus ball of maxillary sinus. Mid Black Sea J Health Sci 2019;5:279-83.
18. Al-Rawee RY, Saeed MM. Challenge dilemma of actinomycosis in the tongue: Review and case report. Int J Surg Case Rep 2020;75:176-81.
19. Nazari DA, Sahab SH, Yahya N, Abdullah MK, Yee LL, Husain S. Fungal septal abscess with maxillary sinus mycetoma in an immunocompetent patient: A rare co existing infection. J Otolaryngol Rhinol 2021;2:46-49.
20. Aggarwal P, Jagati A, Rathod SP, Kalra K, Patel S, Chaudhari M. Clinical features of mycetoma and the appropriate treatment options. Curr Trop Med Rep 2021;12:173-9.
21. Ahmed A, van Leeuwen W, Fahal A, van de Sande W, Verbrugh H, van Belkum A. Mycetoma caused by *Madurella mycetomatis*: A neglected

infectious burden. Lancet Infect Dis 2004;4:566-74.
22. Branscomb R. Mycetoma: An overview. Lab Med 2003;34:803-8.
23. Mallick YA. Eumycetoma due to *Aspergillus niger*: First case report and successful treatment with voriconazole. J Pak Assoc Dermatol 2019;29:428-32.
24. Ali R, Newport M, Bakhiet S, Ibrahim M, Fahal A. Host genetic susceptibility to mycetoma. PLoS Negl Trop Dis 2020;14:e0008053.
25. Verma P, Jha A. Mycetoma: Reviewing a neglected disease. Clin Exp Dermatol 2019;44:123-9.
26. van de Sande W, Fahal A, Goodfellow M, Mahgoub E, Welsh O, Zijlstra E. Merits and pitfalls of currently used diagnostic tools in mycetoma. PLoS Negl Trop Dis 2014;8:e2918.
27. Ahmed A, van de Sande W, Fahal A. Mycetoma laboratory diagnosis: Review article. PLoS Negl Trop Dis 2017;11:e0005638.
28. Mycetoma: Practice Essentials, Background, Pathophysiology; 2021. Available from: https://emedicine.medscape.com/article/211459-overview [Last accessed on 2021 Aug 25].
29. Zijlstra E, van de Sande W, Welsh O, Mahgoub E, Goodfellow M, Fahal A. Mycetoma: A unique neglected tropical disease. Lancet Infect Dis 2016;16:100-12.
30. McGinnis MR. Mycetoma. Dermatol Clin 1996;14:97-104.
31. Kumar J, Kumari A, Garg A, Gupta S. Dot in circle sign in actinomycotic mycetoma on MRI and ultrasound a case series. MAMC J Med Sci 2019;5:145.
32. Jain V, Makwana G, Bahri N, Mathur MK. The "dot in circle" sign on MRI in maduramycosis: A characteristic finding. J Clin Imaging Sci 2012;2:66.
33. Fahal A, Sheik H, Homeida M, Arabi Y, Mahgoub E. Ultrasonographic imaging of mycetoma. Br J Surg1997;84:1120-2.
34. Boiron P, Locci R, Goodfellow M, Gumaa SA, Isik K, Kim B, *et al*. Nocardia, nocardiosis and mycetoma. Med Mycol 1998;36 Suppl 1:26-37.
35. Suleiman S, Wadaella E, Fahal A. The surgical treatment of mycetoma. PLoS Negl Trop Dis 2016;10:e0004690.
36. Welsh O, Al-Abdely H, Salinas-Carmona M, Fahal A. Mycetoma medical therapy. PLoS Negl Trop Dis 2014;8:e3218.
37. Welsh O, Vera-Cabrera L, Welsh E, Salinas M. Actinomycetoma and advances in its treatment. Clin Dermatol 2012;30:372-81.
38. Mahgoub E, Gumaa S. Ketoconazole in the treatment of eumycetoma due to *Madurella mycetomii*. Trans R Soc Trop Med Hyg 1984;78:376-9.
39. de Klerk N, de Vogel C, Fahal A, van Belkum A, van de Sande W. Fructose-bisphosphate aldolase and pyruvate kinase, two novel immunogens in *Madurella mycetomatis*. Med Mycol 2012;50:143-51.