What Can Imaging Do for Mycetoma in an Immunocompetent Patient in Temperate Region

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AUTHORS' CONTRIBUTIONS
Dongming Li designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.
Juan Wu collected pathological data and helped drafting the manuscript.
Yuxiang Liang collected clinical data and helped drafting the manuscript.
Keye Li collected clinical data and reviewed and revised the manuscript.
Ju Zeng collected imaging data and reviewed and revised the manuscript.

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HUMAN AND ANIMAL RIGHTS
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ABSTRACT

Mycetoma is a slowly persistent granulomatous infection of the cutaneous and deep subcutaneous tissue structures. It is caused by true fungi (eumycetoma) or bacteria (actinomycetoma), which is usually endemic in tropical countries. It may be misdiagnosed and delayed by low clinical suspicion, limited availability of diagnostic techniques, lack of biopsy and microbiological culture, potentially leading to disastrous consequences. Therefore, imaging plays a vital role in early recognition as a non-invasive technique, especially Magnetic resonance imaging, which demonstrates a hallmarked "dot-in-circle" sign of mycetoma. In this paper, we will present an immunocompetent patient with nearly two decades of history and review literature to highlight the importance of increasing awareness of mycetoma, particularly in non-endemic regions. The final diagnosis was made based on the characteristic "dot-in-circle" findings on Magnetic resonance images and pathologically confirmed.

CASE REPORT

BACKGROUD

Mycetoma also named Madura foot, is a chronic, progressive, and destructive granulomatous disease involving dermis, epidermis, and fascia. Occasionally it will involve the muscles and tendons, nerves and vessels, and eventually the bones and joints. The infectious microorganisms could be true fungi (eumycetoma) or bacteria (actinomycetoma), which are presumed to be directly inoculated by trivial penetration injury such as thorn or wood splinters. Most mycetoma cases are reported from rural areas of tropical and subtropical countries such as Sudan, India, Mexico, Somalia, Senegal, Yemen etc, which are collectively known as "mycetoma-belt" region [1]. Mycetoma manifests clinically as a classical triad of painless and swelling soft tissue mass, discharging sinus and multicolored grains. Its progression may lead to catastrophic consequences such as deformities, amputations and even high mortality rates, all of which result in a severe economic and social burden. Unfortunately, the incubation period is so prolonged that it usually takes between several months to a few decades to diagnose and begin appropriate chemotherapy or surgery. Magnetic resonance imaging (MRI) offers an early and non-invasive aid to diagnosing mycetoma. The "dot-in-circle" sign is a distinctive MRI finding that is highly specific for diagnosing mycetoma involving soft tissue and bone [2-4]. Here we present

a rare case of mycetoma localized on the foot and ankle of an imnunocompetent patient living in a temperate climate.

CASE REPORT

A 60-year-old male worker from central China (northeast of Sichuan Province) who complained of a painless and progressive mass on his left dorsal foot for almost 20 years. The last 5 years, the patient had suffered from pain and limited mobility, particularly at night. An initial diagnosis at a hospital indicated "left ankle synovitis" with subsequent improvement after left ankle joint effusion aspiration five years ago. Two years ago, recurrence of similar symptoms led to diagnosis of "left ankle arthritis" at another facility. The patient was relieved through analgesic therapy, acupuncture, physiotherapy, and topical drugs. The patient self-treated his symptoms with diclofenac sodium enteric-coated tablets, however the pain increased in frequency and intensity until the patient's sleep was disturbed. Seven months ago, the patient visited another hospital where he was diagnosed with "left ankle tuberculosis". Six months standardized anti-tuberculosis therapy resulted in marginal pain reduction but expanded pain distribution, accompanied by systematic symptoms including subjective high fever and diaphoresis during episodes. He was admitted to our hospital with the diagnosis of chronic osteomyelitis. Physical examination revealed mild muscular atrophy of the left lower limb, a surgical scar, increased skin temperature over the medial aspect of the left foot, significant ankle joint swelling, a 20 × 15cm area of hyperpigmentation on the overlying skin, and desquamation of the epidermis over the medial malleolus and dorsum of the foot (Figure 1). The patient demonstrated reduced active and passive ankle range of motion (ROM). His Visual Analogue Scale (VAS) evaluation was 5 nocturnally and 2 diurnally. Laboratory tests showed elevated levels of C-reactive protein (21.2mg/L), erythrocyte sedimentation rate (76mm/h) and procalcitonin (0.127ng/ml).

Imaging findings

Radiographs showed soft tissue swelling of the dorsal and pedal aspects of the foot, bone erosion, bone sclerosis and thickening, periosteal hyperplasia and osteophytosis of medial malleolus and multiple tarsal bones, accompanied by osteoporosis (Figure 2).

Computed Tomography (CT) revealed significant soft tissue swelling over the medial malleolar and dorsal pedal regions of the left foot, along with irregular cortical thickening and uneven surfaces involving the medial malleolus, talus, navicular bone, medial cuneiform and base of the first metatarsal. A moth-eaten appearance and small cystic osteolytic lesions were observed at the margins and within the osseous structures of these bones. Additional findings included periosteal proliferation, reactive sclerosis, irregular osteophytosis, joint space narrowing of the affected articulations, and generalized osteopenia. CT multiplanar reconstruction (MPR) images provided a comprehensive and detailed view of the lesions (Figure 3).

Magnetic resonance imaging (MRI) demonstrated obvious and extensive subcutaneous soft tissue tumefaction involving the dorsomedial aspect and medial malleolus of the left foot. Additonally, there were multiple, small, rounded lesions of varying sizes (2-4mm) diffusely involving the subcutaneous tissue, muscles, neurovascular bundles, tendons and multiple bones. The lesions were round and nodular on axial images and tortuous linear, and tubular on sagittal images. The lesions were hyperintense with a central hypointense dot and a peripheral rim of low signal intensity on T2-weighted images (T2WI) and fat-suppressed proton weighted images (FS-PDWI) (Figure 4), which revealed classical characteristic of "dot-in-circle" sign. Osseous involvement included medial malleolus, talus, navicular bone, medial, middle and lateral cuneiform, and base of the first metatarsal, all of which showed diffuse marrow edema and periosteal reaction, marginal erosions. Medial cuneiform and navicular bone represented "dot-in-circle" sign particularly. We considered the possibility of chronic infectious lesions based on the imaging findings.

Management and follow-up

The patient underwent a left ankle debridement with partial lesion resection and tissue biopsy; histopathological analysis were performed then. Hematoxylin and Eosin (H&E) staining revealed large fungal colonies surrounded by neutrophilic infiltration and fibrous tissue hyperplasia. Gomori methenamine silver staining demonstrated foci of black fungal hyphae, and Periodic acid-Schiff (PAS) staining showed purple-pigmented colonies of fungal hyphae surrounded by inflammatory cells (Figure 5). The patient refused to do further tests such as polymerase chain reaction (PCR) amplification and DNA gene sequencing studies because of financial reasons.

A multidisciplinary team consultation of radiologist, pathologist and clinical doctors established the definitive diagnosis of Eumycetoma. The patient began to take itraconazole□400mg/day□for antifungal therapy and got clinical symptomatic relief after taking medicine for 6 months. The patient remains on maintenance therapy under close surveillance.

DISCUSSION

Etiology & demographics

Mycetoma infection occurs in humans through the entry of organisms(true fungi in eumycetoma and filamentous bacteria in actinomycetoma) via penetrating wounds from the soil into the skin, subcutaneous tissue, deep structures, and eventually bone and joints.Mycetoma is endemic in many tropical and subtropical countries. It has recently been included in the World Health Organization's list of neglected tropical disease [3,4]. However, it remains a rare and exceptional condition in other regions, including temperate areas of China, where it occurs sporadically and poses diagnostic challenges. As far as we know, only a few cases of mycetoma have been reported in

China up to now [5]. Here we present a rare case of mycetoma localized on the foot and ankle of an imnunocompetent patient living in a temperate climate. This case had never been to a tropical region, he admitted to occasionally working barefoot but could not recall any penetrating injuries. The patient was generally healthy, and had no history of surgery or chronic diseases such as hypertension, diabetes, heart disease, hepatitis B, or other immunosuppressive disorder.

Clinical & imaging findings

Mycetoma manifests clinically as a classical triad of an indolent but progressive subcutaneous mass, formation of draining sinuses and discharge of multicolored granular grains. However, the full presentation of these findings is uncommon, which leads to low clinical suspicion and delayed diagnosis, especially in non-epidemic regions. Our patient had a history of black grains discharge and pale yellow/pink liquid seepage, but both were ignored, resulting in a disease course that extended nearly two decades before a precise diagnosis was finally made—much longer than in many reported cases [3]. The disease is insidious and the incubation period is so prolonged that it usually takes between several months to a few decades to diagnose and begin appropriate chemotherapy or surgery. Thus, a delay in definitive diagnosis and initiation of the treatment can lead to catastrophic consequences such as deformities, amputations and even high mortality rates, all of which result in a severe economic and social burden.

Imaging studies provide a non-invasive aid to the early diagnosis, lesion extent assessment and clinical management planning. Radiographs show soft tissue mass or swelling, bone sclerosis, periosteal reaction, and bone erosion, which may be accompanied by osteoporosis. In addition to periosteal hyperplasia, sclerotic and thickened bone, and slender or irregular osteophytes, obliterated marrow cavities are sometimes observed. CT can demonstrate more detailed features of solitary or multiple bone involvement, including cortical erosion with a moth-eaten appearance and central cavitation, which are indicative of eumycetoma osteomyelitis.

MRI offers an early and non-invasive aid to diagnosing mycetoma and providing valuable information for visualizing both soft tissue involvement and bone destruction. On MRI, T2WI and FS-PDWI images reveal several tiny and rounded hyperintense nodules, hypointense foci within and low signal intensity spherical rims or separation, giving the classical "dot-in-circle" sign [6-8]. This sign has high specificity and sensitivity, and is helpful for the early, noninvasive diagnosis of mycetoma. It was first described by Sarris et al. [6] and is considered a reliable and pathognomonic indicatior for the disease. The central hypointense dot is thought to represent fungal grains affected by magnetic susceptibility, and surrounding hyperintense tissue is the inflammatory granuloma, the peripheral hypointense rim is the fibrous septa [6,7,9]. This "dot-in-circle" sign is clearly visible and characteristic on T2WI, fluid-sensitive, FS-PDWI sequences, and fat-suppressed T1-weighted images (FS-T1WI) with gadolinium enhancement. However, the usefulness of MRI with gadolinium enhancement is very limited, as demonstrated in this case. As mycetoma advances, it could expand from subcutaneous tissue initially to muscles, blood vessels, nerves and tendons and even bones at advanced stages. MRI is the gold standard for evaluating both the soft tissues and bone involvements. When the infection involves osseous structures, MRI demonstrates diffuse bone marrow signal, which may not be apparent on radiographs and CT images. As bone invasion progresses, bone destruction, cavitation, sclerosis, periosteal reaction can be observed on radiographs and CT images. These findings are consistent with osteomyelitis, demonstrating fibrosis indicative of a longstanding process.

A new radiological grading system called "Mycetoma Skin, Muscle, Bone Grading System" (MSMBS) has been proposed by the Mycetoma Research Center of Sudan [10]. It can provide a grade for the the disease severity that can help in planning management and prognosis. The score is based on MRI appearances of the skin, subcutaneous tissue, muscle and bone. According to the system, our patient received a severe grade of 10, which suggests a poor prognosis.

Ultrasonography (US) is also helpful in the early diagnosis and differentiating mycetoma from other conditions. The US findings of "dot-in-circle" sign are very similar to those seen on MRI, with multiple round hypoechoic lesions containing hyperechoic foci corresponding to the grains. Moreover, US can facilitate guided aspiration biopsy and assist in evaluating the extent of the lesion for surgical planning [7,11].

When the clinical history and symptoms raise suspicion, imaging abnormalities especially the characteristic "dot-in-circle" sign on MRI, may suggest a preliminary diagnosis of mycetoma. Definitive diagnosis requires a pathological biopsy to identify the fungi responsible for eumycetoma or actinomycetes associated with actinomycetoma. Microbiological cultures can be performed to confirm the presence of fungal or bacterial pathogens, although many cultures yield negative results. Specific staining techniques, such as Gomori methenamine silver or PAS staining, can be employed to detect fungus when microorganism colonies are observed histopathologically [12]. For precise identification of fungal species, PCR amplification or DNA sequencing is necessary [13]. Unfortunately, these advanced molecular techniques are often inaccessible in developing countries and regions, although this limitation does not hinder appropriate therapeutic choices. Therefore, clinical signs and symptoms, radiological imaging features and histopathological assessment together are extremely important for accurate diagnosis and therapy, follow-up, prognosis management especially when there is suspicion of bone and articular involvement.

Differential diagnoses

Although 80% percent of mycetoma patients present the "dot-in-circle" sign in MRI images, radiologists are required

to differentiate mycetoma from hemangiomas, other soft tissue tumors, and chronic bacterial or tuberculous infections [13].

Treatment & prognosis

Mycetoma remains one of the most neglected infectious diseases worldwide, and eumycetoma is more difficult to treat than actinomycetoma, especially when bone involvement occurs. Treatment for eumycetoma typically includes drug therapy, or a combination of surgical debridement and antifungal drugs. Antifungal treatment for eumycetoma includes itraconazole, ketoconazole, posaconazole, voriconazole, amphotericin B, terbinafine, alone or in any combination, depending on the patient's tolerance [4,14]. When the lesion affects the bones, monotherapy with drugs is no longer adequate. A combination of surgical resection of the lesion tissue and pharmacological treatment becomes essential. In comparison to actinomycetoma, eumycetoma exhibits a relatively lower remission rate and a significantly higher recurrence rate, often ultimately leading to amputation [3,15,16]. Therefore, early diagnosis and recognition of bone involvement is essential to the overall management of eumycetoma.

Mycetoma is not frequently encountered in temperate regions. Imaging, especially MRI, can be a useful technique in the diagnosis of soft tissue masses because of its high soft tissue resolution. When the characteristic "dot-in-circle" sign appears on MRI, the diagnosis of mycetoma should be strongly suspected. MRI can delineate the extent of the infection involvement, help plan surgery and assess clinical efficacy.

Limitations of the present report include the absence of PCR analysis and DNA sequencing.

TEACHING POINT

A diagnosis of mycetoma is to be considered in the list of differential diagnosis for patients with long-standing, painless swelling soft tissue mass of the foot, even from non-endemic areas.

MRI is a useful and noninvasive modality for diagnosing mycetoma involving soft tissue and bone, and the "dot-in-circle" sign is a distinctive MRI finding that is highly specific.

QUESTIONS

Question1: What are the infectious agents that cause mycetoma?

1. Tubercule bacilli.
2. True fungi. (applies)
3. Escherichia coli.
4. Filamentous bacteria. (applies)
5. staphylococcus.

Explanation: Mycetoma is a granulomatous infectious disease divided into two types: eumycetoma, caused by true fungi, and actinomycetoma, caused by filamentous bacteria. [The infectious microorganisms could be true fungi (eumycetoma) or filamentous bacteria (actinomycetoma), which are presumed to be directly inoculated by trivial penetration injury such as thorn or wood splinters.]

Question 2: Which of the following countries is not an endemic region for mycetoma?

1. Yemen.
2. Mexico.
3. Sudan.
4. China. (applies)
5. India.

Explanation: Mycetoma is usually endemic in tropical and subtropical countries, with the highest numbers reported from India, Sudan, Mexico. Rarely, a few cases have also been reported from temperate countries. [Most mycetoma cases are reported from rural areas of tropical and subtropical countries such as Sudan, India, Mexico, Somalia, Senegal, Yemen etc, which are collectively known as "mycetoma-belt" region.]

Question 3: Which part of the human body is the most likely to be affected by mycetoma?

1. Hand.
2. Foot. (applies)
3. Spine.
4. Brain.
5. Thigh.

Explanation: The foot is the most commonly affected site in mycetoma. Most reported cases involve the foot, although there have been a few cases reports involving other parts of body, such as the hand, spine, brain, thigh and so on. [The foot is considered the most common site, however, other sites can be affected as well.]

Question 4: What signs may appear on radiographic and computed tomographic (CT) images when mycetoma infects the bone?

1. Bone destruction. (applies)
2. Bone erosion. (applies)
3. Periosteal reaction. (applies)
4. Bone sclerosis. (applies)
5. Osteoporosis. (applies)

Explanation: When mycetoma infects the bone, it demonstrates imaging features consistent with chronic osteomyelitis. These include bone destruction, moth-eaten bone erosion, bone sclerosis, periosteal reaction and hyperplasia. Osteoporosis may also be present. [Radiographs show soft tissue mass or swelling, bone sclerosis, periosteal reaction, and bone erosion, which may be accompanied by osteoporosis. In addition to periosteal hyperplasia, sclerotic and thickened bone, and slender or irregular osteophytes, obliterated marrow cavities are sometimes observed. CT can demonstrate more detailed features of solitary or multiple bone involvement, including cortical erosion with a moth-eaten appearance and central cavitation, which are indicative of eumycetoma osteomyelitis.] [As bone invasion progresses, bone destruction, cavitation, sclerosis, periosteal reaction can be observed on radiographs and CT images. These findings are consistent with osteomyelitis, demonstrating fibrosis indicative of a longstanding process.]

Question 5: Which of the following statement is false?

1. Clinically, mycetoma presents as a painless subcutaneous mass with draining sinuses and discharge of granular grains.

2. The characteristic "dot-in-circle" sign can be observed on all Magnetic resonance imaging (MRI) sequences. (applies)

3. The "dot" in the "dot-in-circle" sign represents fungal grains.

4. The "circle" in the "dot-in-circle" sign represents fibrous septa.

5. The "dot" in the "dot-in-circle" sign is hypointense on T2-weighted and fat-suppressed proton weighted images (FS-PDWI).

Explanation: 1. The classic clinical triad for diagnosing mycetoma includes a painless, progressive subcutaneous mass, draining sinuses, and granular grains discharge. [Mycetoma manifests clinically as a classical triad of an indolent but progressive subcutaneous mass, formation of draining sinuses and discharge of multicolored granular grains.]

2. The "dot-in-circle" sign is seen on T2-weighted images (T2WI), fluid-sensitive, fat-suppressed proton weighted images (FS-PDWI) sequences, and fat-suppressed T1-weighted images (FS-T1WI) with gadolinium enhancement—but not all MRI sequences. [This "dot-in-circle" sign is clearly visible and characteristic on T2WI, fluid-sensitive, FS-PDWI sequences, and fat-suppressed T1-weighted images (FS-T1WI) with gadolinium enhancement.]

3. The "dot" in the "dot-in-circle" sign represents fungal grains. [The central hypointense dot is thought to represent fungal grains affected by magnetic susceptibility, and surrounding hyperintense tissue is the inflammatory granuloma, the peripheral hypointense rim is the fibrous septa.]

4. The "circle" in the "dot-in-circle" sign corresponds to fibrous septa surrounding the lesion. [The central hypointense dot is thought to represent fungal grains affected by magnetic susceptibility, and surrounding hyperintense tissue is the inflammatory granuloma, the peripheral hypointense rim is the fibrous septa.]

5. The central dot in the "dot-in-circle" sign is low in intensity on T2WI and FS-PDWI sequences due to signal loss from magnetic susceptibility. [The central hypointense dot is thought to represent fungal grains affected by magnetic susceptibility, and surrounding hyperintense tissue is the inflammatory granuloma, the peripheral hypointense rim is the fibrous septa.]

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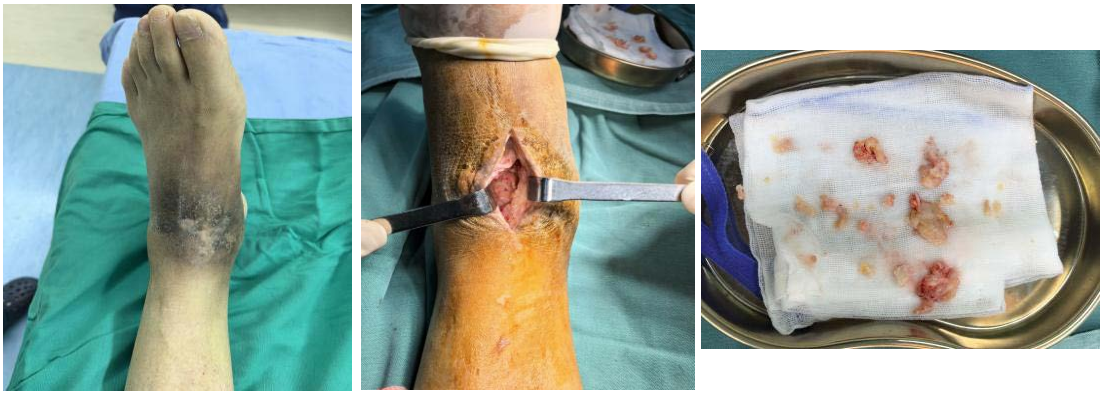
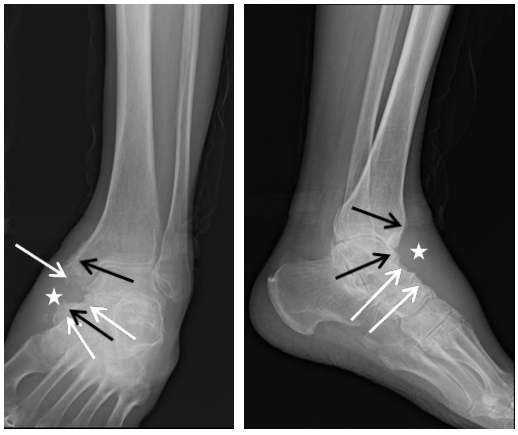
FIGURES



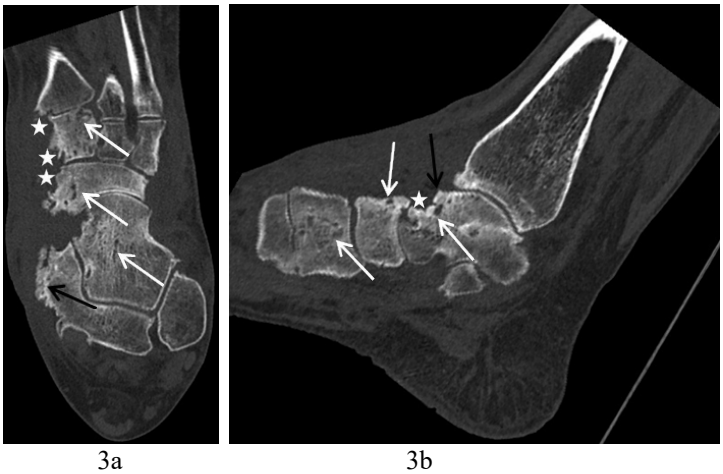
1a 1b 1c

Figure 1: Photographs demonstrate cutaneous hyperpigmentation and crusted sinus tracts (1a), beaded granulomatous nodules of subcutaneous tissue during operation (1b, black arrow), and partial nodular lesions after surgical resection (1c).



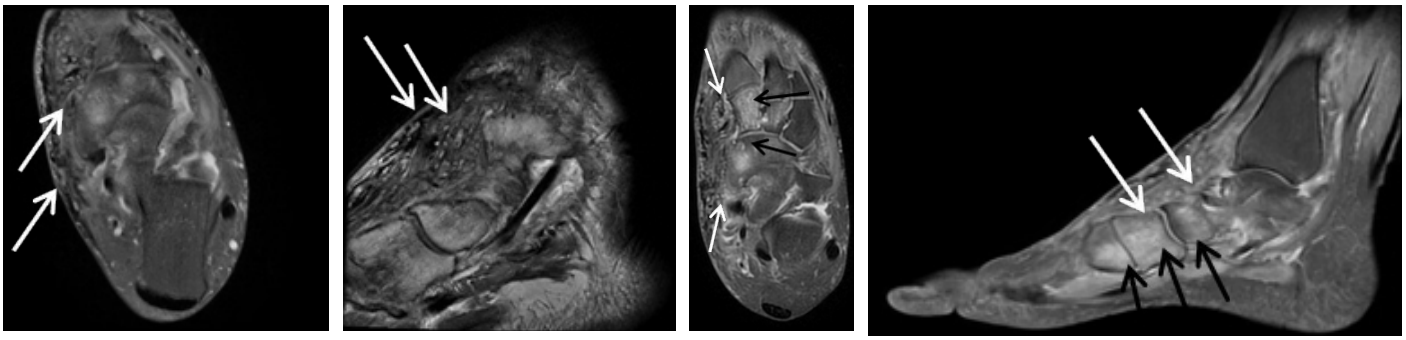
2a 2b

Figure 2: Radiographic images of Mycetoma. FINDINGS: anterior posterior (AP) (2a) and lateral position (2b) radiographs demonstrate soft tissue swelling (asterisk), bone erosion (white arrow), sclerosis, periosteal reaction (black arrow) and osteoporosis. TECHNIQUE: AP and lateral position radiographs, 10mAs, 65kV.



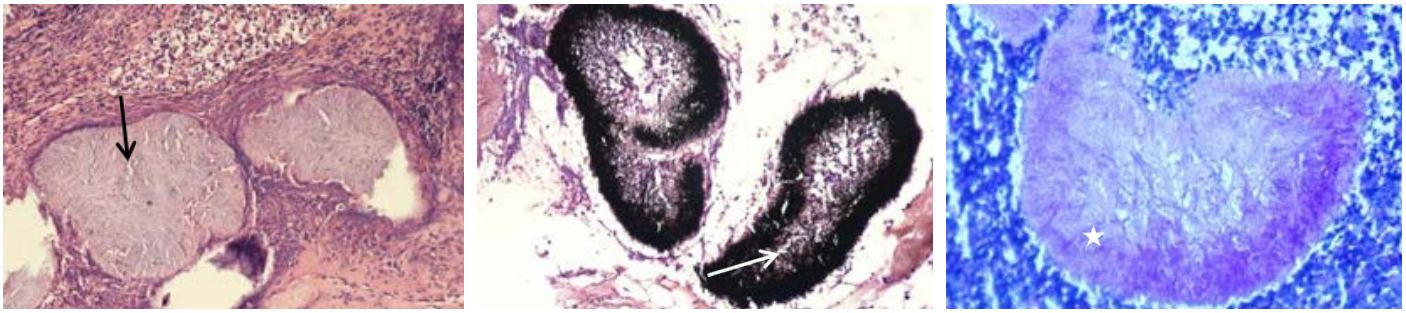
3a 3b

Figure 3: CT images of Mycetoma. FINDINGS: coronal(3a) and sagittal(3b) CT MPR images demonstrate moth-eaten cortical erosion (asterisk) , cystic osteolytic lesions and cavitation (white arrow) of multiple bone involvement, reactive sclerosis, periosteal proliferation (black arrow) and irregular osteophytosis, joint space narrowing and osteopenia. TECHNIQUE: Axial CT, 50mAs, 120kV, 1mm slice thickness.



4a 4b 4c 4d

Figure 4: MRI images of Mycetoma. FINDINGS: FS-PDWI axial (4a) and T2WI sagittal (4b) ankle images show multiple round and nodular hyperintense lesions with a central hypointense dot and a peripheral rim of low signal intensity ("dot-in-circle" sign) (white arrow) of subcutaneous tissue, muscles, neurovascular bundles, tendons and bones. FS-PDWI axial foot image (4c) represents bone erosion and destruction with diffuse marrow edema and "dot-in-circle" sign in multiple bones especially the medial cuneiform and navicular bone (black arrow) , as well as deep subcutaneous tissue lesions of medial foot (white arrow) . FS-PDWI sagittal foot image (4d) demonstrates more advanced erosive destruction and tubular changes in many tarsal bones (black arrow) and the first metatarsal bone as well as generalized deep subcutaneous tissue lesions of the dorsal foot (white arrow). TECHNIQUE: GE SIGNA Architect 3.0T; 4a: FS-PDWI axial TR=3200ms, TE=40ms. 4b: T2WI sagittal TR=5200ms, TE=100ms. 4c: FS-PDWI axial TR=2800ms, TE=40ms. 4d: FS-PDWI sagittal TR=2800ms, TE=40ms. 3mm slice thickness.



5a 5b 5c

Figure 5: Histopathology of Mycetoma. FINDINGS: Fungal colonies are surrounded by neutrophilic infiltration(black arrow), Gomori methenamine silver staining demonstrates foci of black fungal hyphae(white arrow), and PAS staining showed purple-pigmented colonies of fungal hyphae surrounded by inflammatory cells. TECHNIQUE: 5a: H&E staining × 200. 5b: Gomori methenamine silver staining × 200; 5c:PAS staining × 400 .

KEYWORDS

Mycetoma; Madura foot; Eumycetoma; ankle; foot; magnetic resonance imaging; computed tomography

ABBREVIATIONS

ROM = Range of Motion
VAS = Visual Analogue Scale
CT = Computed Tomography
MPR = Multiplanar Reconstruction
MRI = Magnetic Resonance Imaging
T2WI = T2-Weighted Images
FS-PDWI = Fat-Suppressed Proton Weighted Images
FS-T1WI = Fat-Suppressed T1-Weighted Images
H&E = Hematoxylin and Eosin
PAS = Periodic Acid-Schiff
PCR = Polymerase Chain Reaction
MSMBS = Mycetoma Skin, Muscle, Bone Grading System
US = Ultrasonography

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