Madura Foot: A Case Report of a 55-Year- Old Filipino Male

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ABSTRACT

This study aimed to review updates on laboratory tests used for diagnosing along with recent developments in diagnosing and managing eumycetoma.

Reported here is a case of a 55-year-old male with a twenty-six-year history of recurrent left plantar mass associated with discharging black granules and pain on ambulation. The patient was unresponsive to antibacterial and antifungal therapy.

Surgical excision of the mass combined with antifungal therapy using Itraconazole 200 mg twice a day was given post-surgery. Currently, the patient is ambulatory with minimal assistance using the cane. The patient undergoes regular follow-ups and is subjected for re-evaluation after 6 months to re-assess the patient's treatment regimen.

Identification of the microorganism remains to be the cornerstone of treatment. Eumycetoma is frequently neglected and diagnosed at an advanced stage. If left untreated, involvement of underlying tissues such as the bones and muscles could lead to fatal consequences. Therefore, comprehensive clinical examination, using specialized stains, histological and microbiological investigations, and appropriate treatment is recommended to diagnose mycetoma.

Key words: mycetoma, eumycetoma, Madura foot-

Mycetoma, formerly known as "Madura foot", is an endemic disease of tropical and subtropical regions.[1] It commonly affects males between the age of 15-30 years old. It has a 3.7:1, male to female incidence ratio. It affects populations coming from low socioeconomic status such as farmers, field laborers, or herdsmen. Sudan, India, Mexico, Venezuela and Yemen are known as the "Mycetoma belt".[1]

A study in 2020 was made by Denning where only a total of 19,494 recorded cases out of 7.74 Billion in 102 countries were identified from 1876-2020.[2] The most recent Philippine statistics come from 2016. Recording ninety seven cases (97) cases of mycetoma out of 104.9 Million Filipinos.[1]

When in contact with saprophytic soil, the microorganisms are thought to enter the body by traumatic implantation, which occurs when the skin barrier is broken. The organisms then create small microcolonies. It is released onto the skin through sinus tracts and may remain latent for some time. Eventually, it burrows into adjacent tissues, attacking deeper tissues like fascia, muscle, and bone.

Forty percent of cases are caused by filamentous bacteria (actinomycetoma) and sixty percent by true fungi (eumycetoma). Actinomycetoma may be caused by microorganisms such as *Actinomadura madurae, Actinomadura pelletieri, Streptomyces somaliensis, Nocardia species*. While several microorganisms, including *Pseudoallescheria boydii and Acremonium species*, are linked to eumycetoma, *Madurella*

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mycetomatis is the most frequently occurring causative agent. Knowledge of the causative agent is key in the management of the patient.

The disease is characterized by a triad of symptoms which presents as 1) painless subcutaneous lesion, 2) multiple sinuses and fistulas, and 3) discharged granules in pus.

Unfortunately, mycetoma is an insidious disease. Its initial manifestation occurs as a painless lesion and in most cases the disease is left untreated, leading to severe repercussions including physical deformities, disabilities, amputation, and even death.

A study made by Clark, et al in 2024, noted a recurrence rate of 31.8%–46.6% with head and neck mycetoma having a higher recurrence rate of 73.5%.[3]

Differential diagnosis would include cutaneous tuberculosis, osteomyelitis, blastomycosis, dermatophytes or even sarcoma. Histopathological and microbiological examinations help to establish a definitive diagnosis. If diagnosed early, good clinical response with proper pharmacological treatment alone has been reported to be effective.

Presented here is a case of a 55-year-old male patient diagnosed with "mycetoma" from our institution. The patient had a twenty-six-year history of left plantar foot mass associated with discharging black granules and pain on ambulation. The mass was excised for routine histopathology with ancillary stains using Grocott-Gomori stain and Periodic Acid Schiff test. Results showed presence of hyphal elements which are conclusive evidence to the presence of Eumycetoma. The objectives of the study were:

1. To present a case of mycetoma and describe the clinical features, gross, microscopic, and ancillary findings.
2. To discuss the appropriate course of action for the disease's diagnosis
3. To review the current literature on the diagnosis of mycetoma.

THE CASE

This is a case of a 55-year-old male, who presented with a recurrent plantar mass on the left foot. Twenty-six years prior to consult, the patient noticed a fluctuant mass on the plantar aspect of his left foot. (Figure 1) The mass was noted to be approximately 2 cm in size. No other associated symptoms such as pain, discharge, bleeding, and pruritus were noted. The patient does not recall any forms of trauma on the foot. However, the patient reports that during his childhood, he lived in the province of Cagayan and was fond of playing barefooted in the forest until high school. In 1998, the patient initially sought consultation at a private hospital wherein an excision biopsy was done. Histopathology results were reported as "mycetoma" with unremarkable surgical margins. (Figure 2) The mass was noted to be completely excised, hence, no postoperative medications were given.

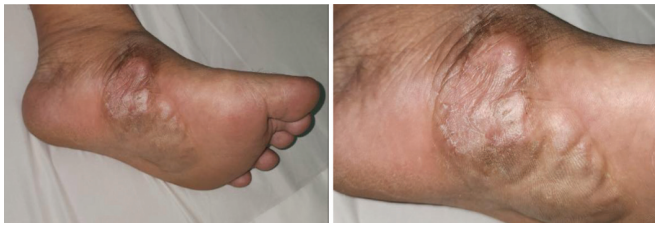

Figure 1. Fluctuant mass on the left plantar aspect of left foot associated with few blackish granular discharges.

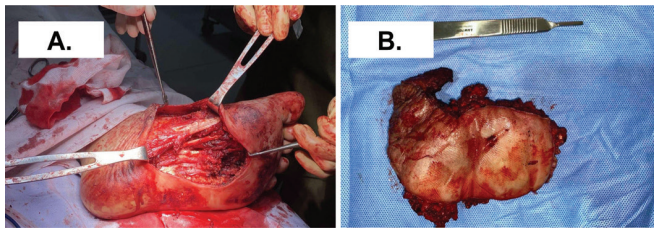

Figure 2: A.) Excision of the mass which revealed the plantar mass with affectation of adjacent tissues and nerves. B.) Excised mass

No masses or growth were observed on the left foot for the next ten years. In 2014, the patient noted a mass-like lesion approximately 5 cm in widest diameter along the medial aspect of the dorsal foot. The patient sought another consultation and was advised to have the mass excised but was lost to follow-up.

One year prior to consultation, the mass was noted to be increasing in size by approximately 8 cm. Few blackish granular discharges and pain upon ambulation were likewise noted. Once again, the patient decided to seek consultation and was advised to have a separate dermatology consult. Initial workup was done which revealed the patient to be a borderline diabetic. Incision Biopsy was done but histopathologic findings only revealed granulation tissue formation and granuloma. (Figure 3) Culture studies were done and no growth was noted in the culture media. The clinician considered that the mass

was bacterial in origin. Empirical treatment consisting of Co-amoxiclav 625 mg/tablet for 6 months was given, however, it did not offer relief of symptoms.

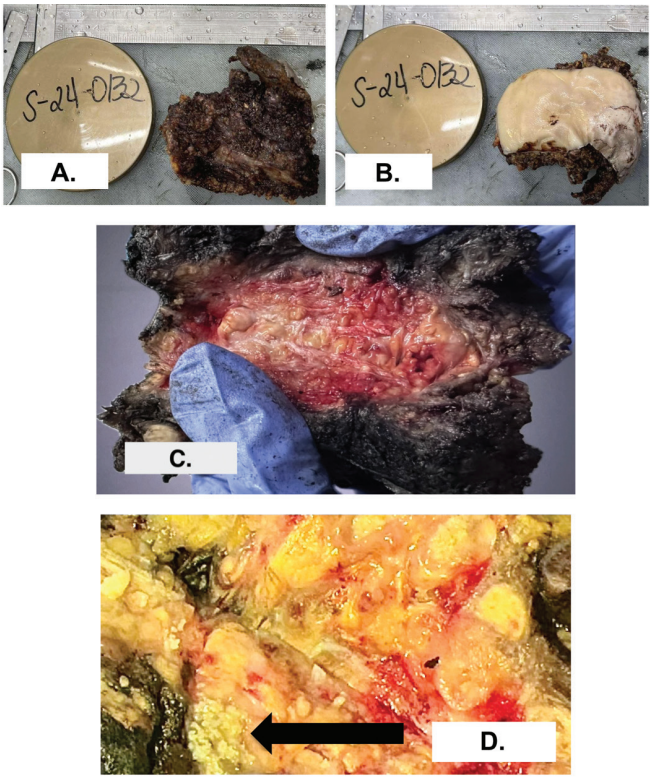

Figure 3. (A. and B.) Gross appearance of the plantar mass submitted for histopathology; (C. and D.) Cut sections of the mass revealed tan-red to tan-yellow cut surfaces with yellow granular material as pointed by the arrow.

Six months prior to consultation, the mass was noted to be increasing in size, now fluctuant, with a mix of firm areas on the foot. Another incision biopsy was done which revealed to be positive for hyphal elements. Grocott-Gomori methenamine silver (GMS) was done and revealed to be positive for fungal elements. Empirical treatment of Itraconazole 200 mg of 1 tablet twice a day for 6 months was given which only minimally decreased the size of the mass.

Two weeks prior to consultation, persistence of symptoms led the patient to seek another consultation. Ultrasound showed underlying muscle involvement of the plantar mass. The patient was advised to have the mass excised. Histopathology revealed the presence of a mycetoma in a background of acute on chronic granulomatous inflammation with granulation tissue and foreign body giant cell formation. Blood vessels also revealed to have possible involvement for fungal elements.

Grossly, the plantar mass was noted to be a tan-brown, irregularly shaped with multiple nodules. Cut sections were made which revealed tan-red to tan-yellow cut surfaces with yellow granular material. (Figure 4)

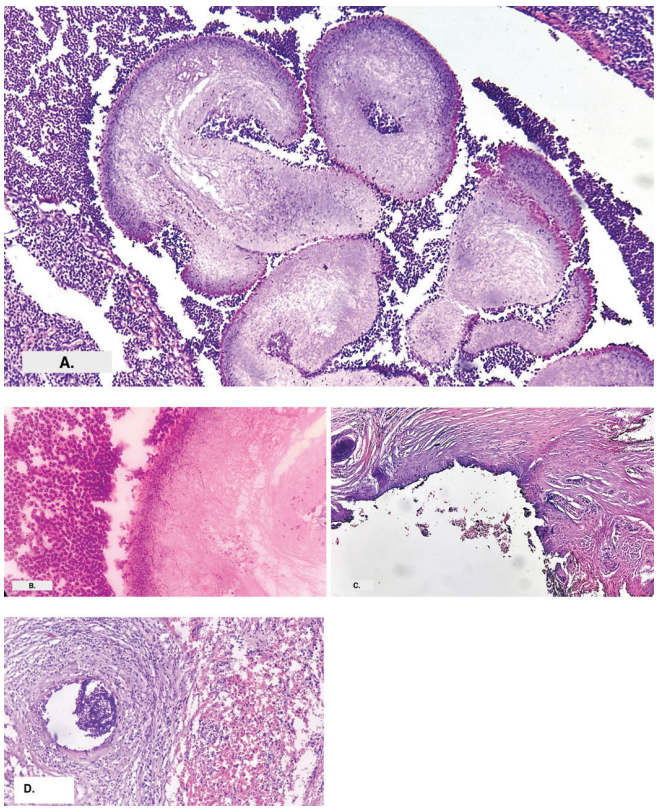

Figure 4. Microscopic images of H and E. (A) Splendore-Hoeppli reaction, LPO; (B) Splendore-Hoeppli reaction, HPO; (C) Acute on chronic inflammation in the inked deep margin. (D) One blood vessel contained inflammatory cells with linear black material.

Microscopically, it revealed the plantar tissue showing amphophilic to basophilic granules surrounded by deeply eosinophilic material, consistent with the Splendore- Hoeppli phenomenon. It is arranged in varisized nodules within cavities in the dermis. (Figure 4)

Splendore-Hoeppli phenomenon or "asteroid bodies" is illustrated by microorganisms surrounded by strong radiating eosinophilic material. Antigen-antibody complexes and debris of host inflammatory cells are thought to be the cause of this reaction.[7] Apart from this reaction, dense collections of neutrophils and lymphocytes with occasional foreign body giant cells and capillaries surrounding the nodules are noted. Granulomas consisting of epithelioid macrophages and lymphocytes are also present. Acute on chronic inflammation was seen in the inked deep

margin. One blood vessel contained inflammatory cells with linear black material. (Figure 4)

Grocott-Gomori methenamine silver (GMS) and Periodic Acid Schiff Test were done which revealed to be positive for hyphal elements. (Figures 5 & 6)

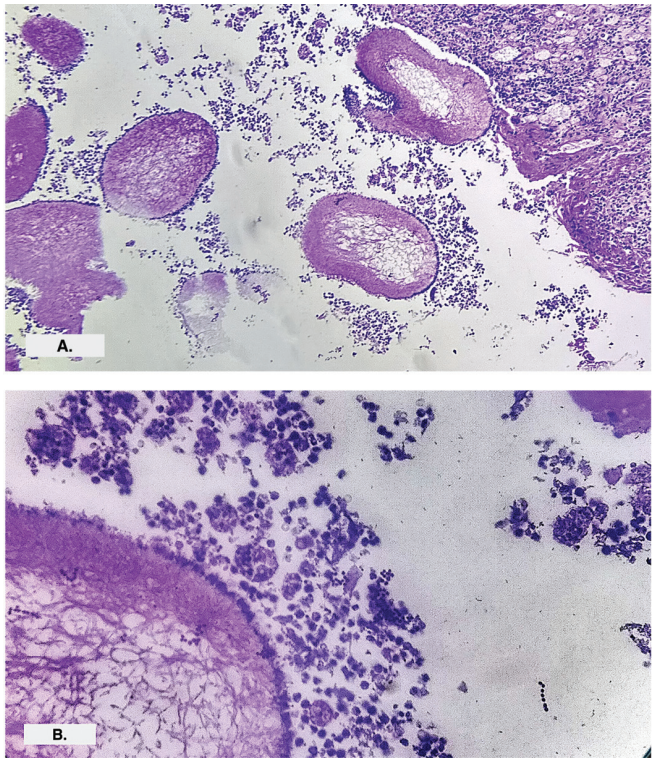

Figure 5. Periodic Acid Schiff Test revealing presence of 2-3 µm delineated, thick, branched, septate fungal hyphae confirming the diagnosis of Eumycetoma. (A) LPO; (B) HPO.

Post-surgery, the patient was given Itraconazole 200 mg of 1 tablet twice daily for six months and zinc supplements with 30 mg once a day. Regular follow-ups under the service of surgery and dermatology were done. Serial monitoring of liver function tests and blood sugar control was done.

The patient subsequently underwent another ultrasound which revealed results of residual or recurrent lesions of mycetoma in the left foot; Post-operative subcutaneous edema and granulation reaction. (Figure 7) MRI with contrast was also done which revealed a result of histopathology confirmed intramuscular mycetoma; Osteolytic changes of the 1st, 4th and 5th proximal phalanges, 5th intermediate and distal phalanges; Subcutaneous edema and fasciitis; Tendinopathy, tibialis posterior, flexor digitorum longus and extensor digitorum longus of the 1st, flexor digitorum brevis of the 3rd to 5th digits and peroneus brevis tendons. Re-evaluation after 6 months

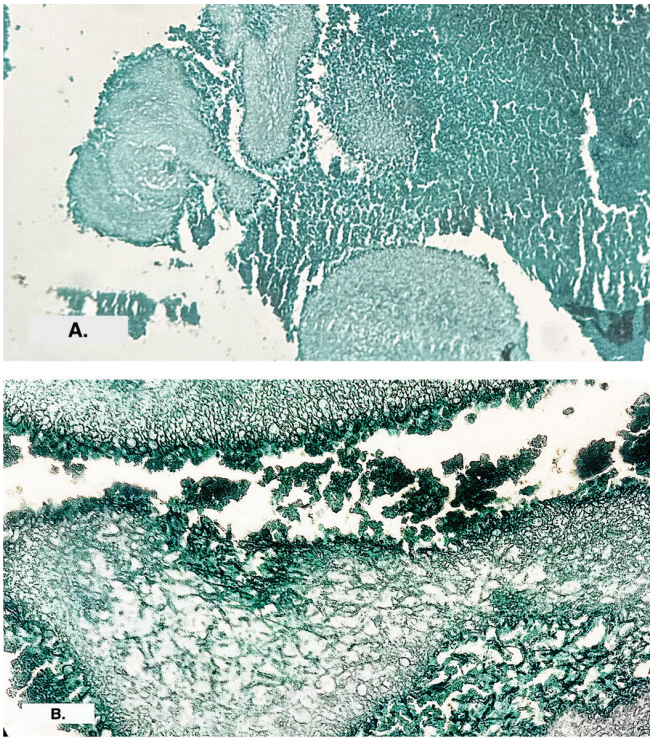

Figure 6. Grocott-Gomori Stain revealing presence of 2-3 µm delineated, thick, branched, septate fungal hyphae confirming the diagnosis of Eumycetoma. (A) LPO; (B) HPO.

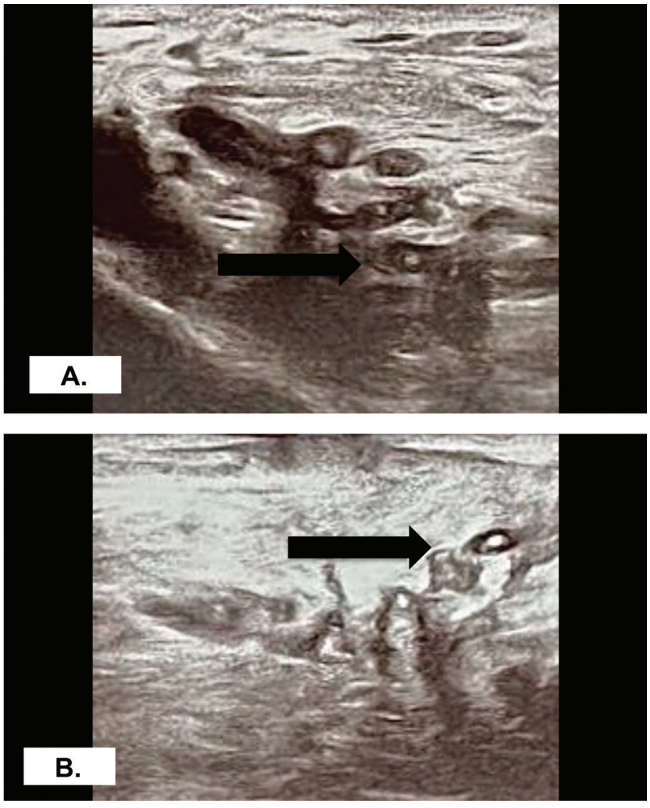

Figure 7. Ultrasonography finding of the patient's left foot from the left medial, inframalleolar showing the classic "dot in a circle" sign.

was recommended to re-assess the patient's treatment regimen. Currently, the patient is ambulatory with minimal assistance using the cane.

DISCUSSION

The case is a 55-year-old male who presented with a twenty-six-year history of recurrent plantar mass on the left foot. The risk factor that can be linked to this case is that it commonly affects young adults between the ages of 16–40 years old.[4] Low socioeconomic status is one of the most attributable causes. It leads to malnutrition and poor general health, which makes a person more susceptible to develop the disease. The patient does not recall any forms of trauma on the foot, however, during his childhood years, the patient was fond of playing barefooted in the forest. Among the risk factors, the mass was first noted at the age of twenty-nine. No history of trauma was noted but prolonged exposure to saprophytic soil early in his childhood predisposes the patient to develop the disease.

In vitro, both fungal and actinomycotic antigens are thought to cause complement- dependent chemotaxis of polymorphonuclear leukocytes.[4] The innate immune system would typically try to engulf and neutralize these organisms under normal circumstances. T-cell responses appear to be important in the development of mycetoma. Certain lesions and draining lymph nodes exhibited Th2-like responses, such as interleukin (IL)- 10 and IL-4. IL-10 acts by impairing the antifungal effector functions of phagocytes, secretion of proinflammatory cytokines and production of Th1-promoting cytokines. Both the acute phase of infection and healthy endemic controls exhibit the responses.[5]

A study conducted by Salinas-Carmona in 2004, has shown humoral antibodies also play a role in mycetoma. IgM antibodies were seen to be protective against N. brasiliensis infection. The slow onset and the delay in development of actinomycetoma were attributed to the disappearance of IgM antibodies and the appearance of IgG.[6]

The disease is still relatively uncommon in the Philippines. Hence, it is commonly misdiagnosed. An interplay between competent histopathologists, accessible microbiologic and fungal studies, appropriate ancillary testing, and appropriate imaging modalities should be used in order to arrive at a conclusive diagnosis and create the most effective treatment plan.

The best method for diagnosing mycetoma is through direct clinical examination, microscopy, gram staining and culture studies. Assessing the size, color, and consistency variations in the grains is part of the direct clinical examination, and it can be useful in quickly but provisionally identifying the etiological agent.[7] Actinomycetoma's thin filaments and eumycetoma's thicker hyphae are distinguished by unique analysis on crushed granules using lactophenol blue.

Table 1. Showing the comparison of Actinomycetoma and Eumycetoma on direct microscopy[20]

	Actinomycetoma Gram-positive	Eumycetoma Gram-negative
Grain color	Yellow, red, pink, white	Black, pale, white, yellow
Grain size	Smaller (0.2-1 um)	Larger (2-5 um) wide hyphae
Grain texture	Septate fine-branching filaments	Coarse, Septate hyphae
Sinus (Number, Morphology)	Many sinuses, flat	Few sinuses, prominent
Stains	Gram stain	Grocott-Gomori methenamine silver (GMS) and Periodic Acid Schiff Test

Table 2. Showing the different findings presented by the patient

Grain color:	Yellow to black
Grain size:	2-3 µm
Grain texture:	Delineated, thick, branched, septate hyphae
Sinus:	Few sinuses
Stains:	Grocott-Gomori methenamine silver (GMS) and Periodic Acid Schiff Test were done and confirmed the diagnosis of Eumycetoma.

Histopathology was done since the patient was generally unresponsive to medical management. The definitive management for eumycetoma should consist of complete surgical excision in combination with prolonged antifungal regimen.

In eumycetomas, apart from H and E, periodic acid–Schiff and Grocott–Gomori staining may be performed for finer details. When an actinomycetoma is suspected, an additional Gram staining should be performed. Periodic acid Schiff (PAS) stains and Grocott-Gomori provided excellent contrast and showed 2-3 μm delineated, thick, branched, septate fungal hyphae in the tissue. PAS colored the cells in magenta because it reacts with glycogen, mucin, and neutral polysaccharides present in fungal cell walls. GMS on the other hand, stained the fungal elements in black which confirmed the diagnosis of eumycetoma. In conclusion, the diagnosis of eumycetoma was confirmed.

Despite having high diagnostic specificity, culture studies were not performed on the sample because it was submerged in formalin. The patient was already experiencing difficulties with activities of daily living, specifically, with ambulation, hence, excision biopsy was recommended.

The causative microorganism of eumycetoma known as M. mycetomatis grows at an extremely slow rate. Specialized media like dextrose agar, Kimmig's agar, or Sabouraud 4% are used as culture media. To ensure that slow growing fungi are not overlooked, culture growth of around 4-6 weeks is performed. Initial colonies do not begin to develop until ten to fifteen days into cultivation.

According to the histopathology report, suspicious fungal elements within the blood vessels were also noted. (Figure 4) Diagnostic modalities such as ultrasonography enable the assessment of disease extent involving the bone. Sonographic findings showed a heterogeneously echogenic granulation tissues along the medial aspect of foot with minimal cobble-stoning pattern. Areas with very hypoechoic ovoid lesions with central hyperechoic focus, exhibiting a "dot-in-circle" sign, tracking along the medial aspect of the foot which is present in mycetoma. (Figure 7) Ultrasonography successfully differentiates the mycetoma from osteomyelitis. Single or multiple thick-walled cavities with distinct hyper-reflective echoes with no acoustic enhancement are produced by Eumycetoma. Actinomycetoma yielded comparable outcomes, with the exception that grains generated tiny echoes that were located at the bottom of cavities.[9]

Recent discoveries have demonstrated that computerized tomography can offer comprehensive evaluations of visceral and soft tissue involvement, however, magnetic resonance imaging (MRI) remains the imaging of choice for assessment of the bone and soft tissue involved known as "dot-in-circle sign".[10] On T2-weighted imaging, the dots hypointense foci within spherical, high-intensity lesions, surrounded by low-intensity matrix. The dots and circles represent the grains and granulomas dispersed in fibrosis-affected areas, respectively.[10] MRI with contrast was done to evaluate the extent of bone and muscular involvement. The results revealed, enhancing marrow abnormalities with periosteal reaction and sclerotic changes are the patient's foot. Enhancing reticular T2W hyperintensities are seen in the cutaneous, subcutaneous, and fascial layers surrounding the fore- to midfoot.

Table 3. Summary of diagnostic procedures for mycetoma

Method	Eumycetoma	Actinomycetoma
Direct Microscopy	Coarse grains 0.5-2mm	Fine 20-100μm
Histopathology	Larger Septate hyphae 4-5μm thick	Smaller Fine branching filaments <1μm thick
Culture	Gram Negative	Gram Positive/Negative
Radiology	Single or multiple thick-walled cavities, without acoustic enhancement	Grains demonstrate distinct hyperreflective echoes
Ultrasonography	Hyperechogenic	Less echogenic
MRI	"dot-in-circle sign"	"dot-in-circle sign"

Table 4. Showing the different findings presented by the patient

Direct Microscopy:	Grocott-Gomori methenamine silver (GMS) was done which was revealed to be positive for fungal elements.
Histopathology:	Histomorphologic analysis revealed the presence of a mycetoma in a background of acute on chronic granulomatous inflammation with granulation tissue and foreign body giant cell formation. Histopathologic examination of the blood vessels also revealed possible involvement of the fungal elements.
Culture:	Not done • Specimen submitted was submerged in formalin: Unsuitable for microbiological studies **Previous culture studies done in 2023**: No growth was noted in the culture media.
Radiology:	Not done
Ultrasonography:	Heterogeneously echogenic granulation tissues; Cobble-stoning pattern; "dot-in-circle"
MRI with doppler:	Enhancing marrow abnormalities with periosteal reaction and sclerotic changes

The preferred treatment of choice for eumycetoma is surgical excision with prolonged use of antifungals, such as itraconazole according to Mycetoma Research Center- Evidence based guidelines for the management of mycetoma patients. A two- year course of treatment is typically needed, but it is important to assess the patient's response and side effects periodically.[11]

The current treatment regimen of the patient includes medical management with Itraconazole 200 mg of 1 tablet twice a day and zinc supplements with 30 mg once a day with regular follow up checkups for six months. Serial monitoring of liver function tests and blood sugar control is also done. Currently, the patient is ambulatory with an assistive device using a cane. He is also subjected for referral to rehabilitation medicine and physical therapy services to address his gait and complaints of residual pains.

SUMMARY AND CONCLUSION

Mycetoma is a rare, often neglected disease in tropical and subtropical countries. Presented here is a case of a 55-year-old male, with a recurrent plantar mass on the left foot for twenty-six years. Excision biopsy with a histopathology together with Grocott-Gomori methenamine silver (GMS) and Periodic Acid Schiff Test and confirmed the diagnosis of Madura foot or Eumycetoma.

If there is strong clinical suspicion, mycetoma can be identified solely by direct microscopy. Appropriate specimen collection for all tests should include pus from draining sinuses or abscesses or tissue obtained for direct microscopy, culture studies, and biopsy. Initial culture studies and biopsy of the patient upon the recurrence of mass might have been incorrectly done, leading to an erroneous result.

Unfortunately misinterpretation of infectious diseases is still common in the Philippines. Fungal infections in particular are often misdiagnosed as cancer or another infectious disease. An interplay between clinical correlation, histomorphology and microbiologic studies are critical to arrive at a diagnosis of eumycetoma because if left untreated, can lead to fatal consequences.

Therefore, mycetoma need to be accurately diagnosed after a comprehensive clinical examination, using specialized stains, histological and microbiological investigations, and appropriate treatment.

LIMITATIONS

Fungal culture and sensitivity testing are very helpful in establishing the diagnosis of Madura foot cases but in our case, the specimen was submitted already fixed and submerged in formalin making it unsuitable for microbiological studies.

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REFERENCES

1. Nazimuddin M, et al,. The Madura foot - A case report. 2011.
2. Global burden of human mycetoma: A systematic review and meta-analysis. PLoS Negl Trop Dis 2013; 7(11): e2550. doi:10.1371/journal.pntd.0002550.
3. Julia E Clark, et. al, Eumycetoma causative agents: A systematic review to inform the World Health Organization priority list of fungal pathogens, Med Mycol 2024; 62(6).
4. Yousif MA, Hay RJ. Leucocyte chemotaxis to mycetoma agents – The effect of the antifungal drugs griseofulvin and ketoconazole. Trans R Soc Trop Med Hyg 1987; 81: 319–21.
5. el Hassan AM, Fahal AH, Ahmed AO, Ismail A, Veress B. The immunopathology of actinomycetoma lesions caused by Streptomyces somaliensis. Trans R Soc Trop Med Hyg 2001;95:89–92.
6. Salinas-Carmona MC, Pérez-Rivera I. Humoral immunity through immunoglobulin M protects mice from an experimental actinomycetoma infection by Nocardia brasiliensis. Infect Immunol 2004;72:5597–604.
7. Gopinath D. Splendore-Hoeppli phenomenon. J Oral Maxillofac Pathol 2018 May- Aug;22(2):161-2. doi: 10.4103/jomfp.JOMFP_79_18.
8. Salinas-Carmona MC, Welsh O, Casillas SM. Enzyme-linked immunosorbent assay for serological diagnosis of Nocardia brasiliensis and clinical correlation with mycetoma infections. J Clin Microbiol 1993; 31: 2901–6.
9. Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: Fungal tropical diseases. J Am Acad Dermatol 2005; 53: 931–51.

8. Salinas-Carmona MC, Welsh O, Casillas SM. Enzyme-linked immunosorbent assay for serological diagnosis of Nocardia brasiliensis and clinical correlation with mycetoma infections. J Clin Microbiol 1993; 31: 2901–6.
9. Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: Fungal tropical diseases. J Am Acad Dermatol 2005; 53: 931–51.

10. Sarris I, Berendt AR, Athanasous N, Ostlere SJ OSIRIS Collaborative Study Group. MRI of mycetoma of the foot: Two cases demonstrating the dot-in-circle sign. Skeletal Radiol 2003; 32: 179–83.
11. Fahal A & Ali H. Why is mycetoma still a public health dilemma 2022; 15: 1990-9.