DOI: https://doi.org/10.3126/njdvl.v21i1.51677

A Neglected Swollen Limb: Resurgence or Common Tropical Disease?

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Abstract

Mycetoma is uncommon, chronic granulomatous infection caused either by fungi or by aerobic filamentous actinomycetes bacteria which is characterized by a triad of painless subcutaneous mass, multiple sinuses and discharge containing grains. We report a case of 40 years old male, farmer who presented with multiple painless swollen lesions over right foot for 8 years. Swelling had gradually increased in size over a few years followed by multiple episodes of discharge. It had not restricted his daily activities. On examination, there were multiple nodules and sinuses discharging serous fluid from the right foot. Gram staining of discharge showed gram positive filamentous rods and KOH was negative. Histopathology showed multiple granulomas. Patient was treated for five cycles using modified Welsh regimen. Patient was assessed by measuring girth of foot and number of lesions in each visit and showed significant improvement at the end of fifth cycle.Patient was followed for one year after treatment without any recurrence.

Key words: Bacteria; Fungi; Granuloma

Introduction

Mycetoma is neglected tropical disease.[1] It is also called as "Madura foot".[2] It is localized, slowly progressing, chronic granulomatous infection of skin and subcutaneous tissue caused by filamentous fungi or aerobic actinomycetes bacteria.1 It can also affect deeper underlying structures like fascia and bones if remains untreated. It is characterized by triad of tumefaction, underlying sinus tracts and grains or granules containing aggregates of causative organism which is discharged from those multiple sinuses on skin surface.[3,4] Actinomycetoma comprises approximately 60% of cases of mycetoma. It mostly affects farmers, field workers or people walking barefoot. Bacteria usually enter the host skin mostly in foot via traumatic implantation such as thorn pricks or splinters.[1,2] In comparison to eumycetoma, actinomycetoma tends to progress more rapidly with extensive tissue inflammation, destruction and early involvement of underlying structures like bone.[5] The incubation period varies from three months to nine years so patient usually does not recall the history of trauma. Patients usually presents with swelling of the affected site with multiple sinuses discharging granules.[1,4] We report this case from Nepal which will help clinician to diagnose such neglected tropical disease at an early stage to have prompt treatment and avoid complications.

Case presentation

A 40-year-old male, farmer by occupationpresented with complaints of multiple painless swollen lesions over right foot for 8 years. Lesion was initially of a size of small pea with firm consistency which gradually increased in size within a week. It was associated with mild itching. There was no history of associated pain and burning sensation in the lesion. Lesion over a period of few weeks developed multiple discharging sinuses on dorsum of right foot. Discharge was thin, seropurulent, pale to white in colour. There were multiple healed lesions with scarring and pigmentation over dorsum of right foot. New lesions continued to appear without the episodes of symptom free interval.

Funding: None
Conflict of Interest: None

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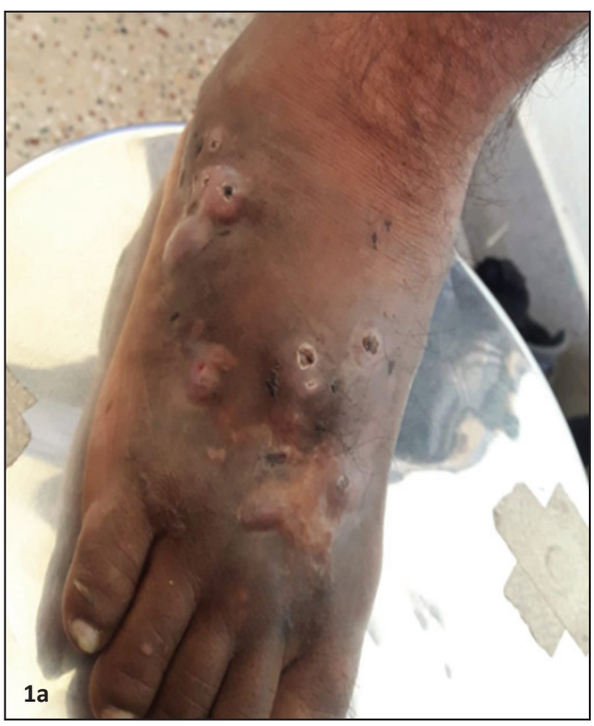
Date of Submission: 10th January 2023
Date of Acceptance: 11th March 2023
Date of Publication: 1st April 2023

How to cite this article
Ray S, Thapa DP. A Neglected Swollen Limb: Resurgence or Common Tropical Disease? NJDVL 2023;21(1):45–49. https://doi.org/10.3126/njdvl.v21i1.51677

After a long painless period of 7 years, he gradually started to develop pain over the heel of right foot which was insidious in onset, non-radiating, pricking in character and aggravated on walking long distance. Pain was relieved by rest. Patient could not recall the history of local trauma. On cutaneous examination, there was diffuse swelling of right foot with multiple non-tender erythematous crusted papules, few coalescing to form plaques and nodules on dorsum of right foot with few areas of hypopigmentation and hyperpigmentation. Later lesions also involved lateral and plantar aspect of right foot. There were multiple discharging sinuses present on the nodule without any discharge. Sites were cleaned with normal saline and peripheries of the active sinuses were pressed. Serous discharge with yellowish white granules exuded from the sinuses. Girth of the fore foot, mid foot and hind foot of right side in its maximum dimension were measured during each visit at the end of cycle to assess the improvement. Girth of fore foot was 20.9cm, mid foot was 26.3cm and hind foot was 29.2cm before treatment. A provisional diagnosis of Mycetoma was made.



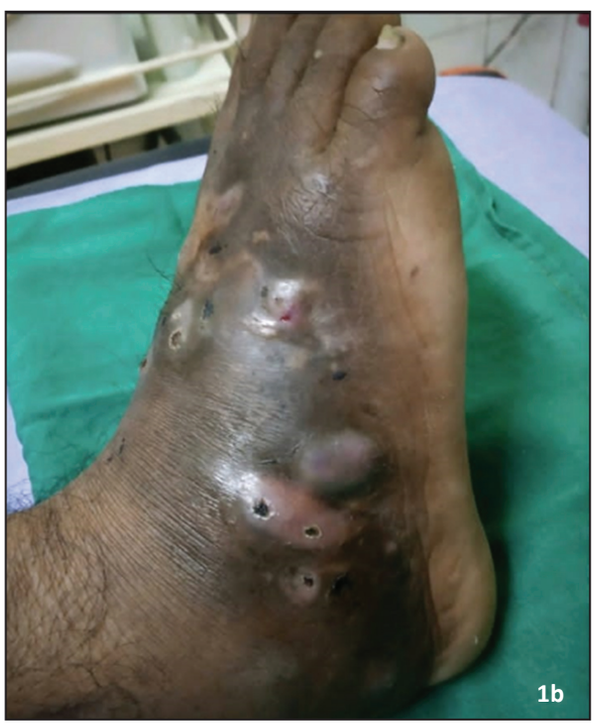


Figure 1a, Figure1b: Foot affected with actinomycetoma showing multiple nodules, sinuses and old healed lesion

Discharge was sent for KOH mount and gram stain. KOH mount was negative but gram staining showed gram-positive rods suggesting actinomycetoma as shown in Figure 2. Other baseline investigations like complete blood count, liver function test, renal function test, random blood sugar and urine routine examinations were sent which were normal. Ultrasonography of right foot showed multiple cavities with collections with edema of subcutaneous tissue giving rise to cobblestone appearance.Histopathological examinationrevealed suppurative granuloma consisting of predominantly neutrophils along with lymphocytes,macrophagesand melanophages.Congested blood vessels along with extravasation of RBCs are seen in deeper dermis layer.

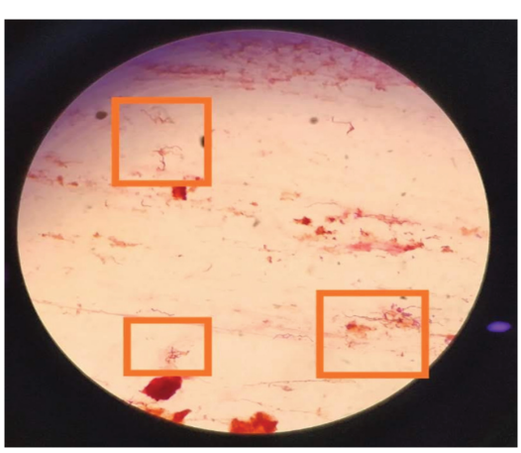


Figure 2: Filamentous gram-positive bacteria in gram stain as shown in yellow boxes.

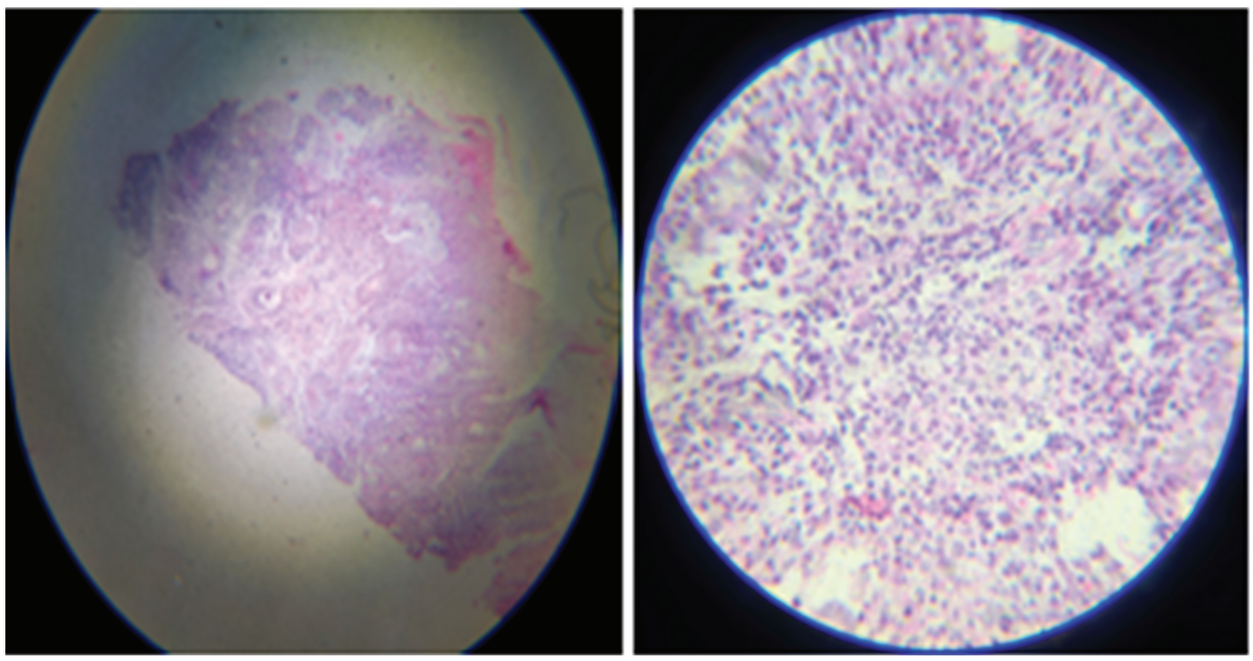


Figure 3a, Figure 3b: Histopathological examination showing multiple granulomas in 4X magnification in H and E stain in figure 3a and multiple inflammatory cells including neutrophils, lymphocytes and macrophages in 40X magnification in the figure 3b.

A diagnosis of actinomycetoma was made and patient was treated using modified Welsh regimen6 with Amikacin 750mg intravenously once a day, oral Cotrimoxazole 960mg twice daily and oral Rifampicin 600mg once daily along with oral iron and folic acid supplementation continuously for 21days which constituted 1 cycle.Five cycles were given with interval of 15 days between each cycle. Oral cotrimoxazole, rifampicin and iron were given uninterruptedly throughout the cycle and were continued for more 2 months after completion of fifth cycle.

Follow up and outcome

Patient was admitted 5 times for modified Welsh regimen as lesion healed completely after fifth cycle and patient was followed for one year after treatment without any recurrence. Patient improvement was assessed by counting the number of lesions and measuring the girth of affected foot as shown in Table 1.

Number of cycles	Pretreatment	First cycle	Second cycle	Third cycle	Fourth cycle	Fifth cycle
Number of lesions	12	12	10	6	4	2
Girth of forefoot	20.9cm	20.8cm	19.8cm	19cm	19cm	19cm
Girth of midfoot	26.3cm	26.1cm	23.4cm	21.5cm	21cm	20cm
Girth of hindfoot	29.2cm	29.2cm	29.1cm	28.9cm	28.8cm	28cm

Table 1: Number of lesions and girth of right foot at each visit

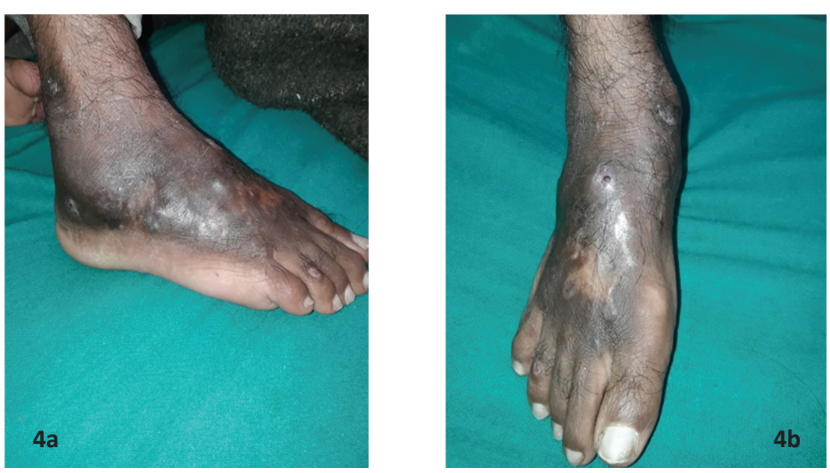


Figure 4a, Figure 4b: Right foot post treatment after 4th cycle

Discussion

World-wide reported frequency of mycetoma shows 60% of cases are bacterial in origin whereas fungi are responsible for 40% of cases.[7] Mycetoma can occur in any part of the world but it is endemic in tropical and subtropical region with hot and humid climate with intermittent short periods of rainfall.[1] Actinomycetoma is more prevalent in drier areas, whereas eumycetoma is more common in sites with more rainfall.[4]

Mycetoma usually affects men in third to fourth decade of life who are actively engaged in outdoor work like farmers, labourers and herdsmen.[8] The most common site involved is foot followed by hand but it can also affect other body parts like arm, forearm, abdomen, thorax, back head and neck.[9] Mode of transmission is traumatic implantation of the causative organism from the contaminated soil to skin via thorn prick or splinter.[1] Regarding the pathogenesis, pathogen after entering the host tissue, innate immune system of the body attempts to engulf and inactivate the pathogens but is unable to do so producing three types of immune response.[2] Firstly, degranulated neutrophils adheres to the grain surface which is surrounded by zone of granulation tissue containing macrophages, lymphocytes, and plasma cells. Secondly neutrophil disappears and macrophage arrives to clear it. Thirdly, there is formation of epitheloid cell granulomas.[4]

Actinomycetoma produces grain of white and yellow color like in our patient but red to pink color grains are found in *Actinomadurapelletieri*. Its size is <1µm, thin and numerous with fringes.[1] Eumycetoma usually produces grain of black or brown color but in case of Acremonium, Fusarium and Scedosporium white to pale yellow grains are found.[4] Size of grains measures > 3 µm of diameter, with few thick hyphae dilated in places to form vesicles with no fringes.[1] Lymphatic extension has been reported in few cases, as in our patient who presented with right inguinal lymphadenopathy.[10]

Gram staining of the granules shows gram-positive fine filamentous bacteria like in our patient in case of actinomycetoma. In case of eumycetoma thick septate hyphae can be found on KOH mount.4 Period acid Schiff method can also be used to stain filaments in eumycetoma. Size of the filaments, septation, morphological characteristics, and pigment formation are used to differentiate between actinomycetoma and eumycetoma.1 First case was reported from Laos, Southeast Asia. Gram staining revealed gram-positive filamentous bacteria which grew on chocolate and blood agar after 5 days and it was subsequently identified as *Actinomaduramadurae* by 16S rRNA gene amplification and sequencing.[5] Likewise in another case reported from Chhatisgarh, India,yellowish grains were collected and cultured on Sabourads Dextrose Agar, Brain heart infusion agar and Lowenstein Jensen media (LJ media). After 5 weeks of incubation, dark magneta pink colonies appeared on LJ media which showed thin branching filaments not more than 1µm on gram staining. In this study only genus *Actinomadura* was identified and species could notbe identified.[2] Ultrasound imaging is done to accurately define the extent of the lesion. Presence of grains can be shown by sharp hyper-reflective echoes. Cavities with or without acoustic enhancement is seen in eumycetoma, whereas in actinomycetoma, the grains are less distinct because of their smaller size.[1]

Deep punch biopsy should be taken to include the subcutaneous tissue and H and E staining is done and visualized under microscope. It shows suppurative granuloma composed of neutrophils surrounding the grains which in turn is surrounded by palisading histiocytes and mixed inflammatory infiltrate composed of lymphocytes, plasma cells, eosinophils and macrophages.[1,4] In our case also we saw suppurative granuloma with inflammatory infiltrate consisting of neutrophils, lymphocytes and macrophages.

As compared to eumycetoma, actinomycetoma is more responsive to medical treatment. Thevariety of antibiotics used in the past for actinomycetoma weresulfonamides, isoniazid, streptomycin, tetracycline, cotrimoxazole, amikacin, gentamicin, amoxicillin-clavulanic acid, imipenem, and rifampicin.[6] Combination therapy were used which prevented from the drug resistance and was successful in eradicating the residual infection.[4] Welsh *et al*. in 1987 used the combination of amikacin and co-trimoxazole to treat the 15 cases of actinomycetoma. This Welsh regimen included cyclical dosing of amikacin 15 mg/kg/day intravenously in two divided doses in cycles of 21 days for 1–3 cycles with intervals of 15 days between cycles while cotrimoxazole double strength tablet was administered twice a day continuously for 35–105 days. The 2-week interval of amikacin was used for renal and audiometric monitoring. All patients achieved remission with this regimen with most patients requiring two cycles (42 days) of amikacin and 70 days of cotrimoxazole therapy.[11] Damle*et al*. in 2008 introduced the modified Welsh regimen in unresponsive patients by adding rifampicin at the dose of 10mg/kg/day as the third drug. They used this regimen to treat 18 patients of actinomycetoma out of which only 16 patients completed the treatment. Out of them 10 patients showed significant improvement after 3 cycles whereas 6 patients were treated for 4 cycles. Co-trimoxazole and rifampicin was given uninterruptedly for 3 months after the last amikacin cycle.[6] Ramam*et al*. used a 2-step regimen consisting of an intensive phase with cotrimoxazole, penicillin, and gentamicin for 5 to 7 weeks, followed by maintenance therapy with amoxicillin and co-trimoxazole for 5-6 months after complete remission.[12] We also opted for modifiedWelsh regimen. Amikacin 750mg was given intravenously once a day for 21 days which constituted 1 cycle and next cycle was started after the interval of 15 days. Our patient was administered 5 cycles of amikacin. Oral Co-trimoxazole 960mg was given twice

a day and rifampicin 600mg was given once a dayalong with iron supplement throughout the treatment. Oral medications were continued up to 2 months after the completion of fifth cycle.

Conclusion

Mycetoma is a chronic granulomatous infectious disease which runs a long course due to its painless nature. It mostly affects a person of low socio-economic condition who works barefoot. Course may be fatal if not treated on time. Treating physician might face difficulties regarding the compliance of treatment due to prolonged course of treatment. We report this neglected tropical disease of Actinomycetoma to create awareness among treating physician for early detection with the aid of simple laboratory diagnostic procedure such as gram stain along with histopathology and radiological diagnostic tool with early treatment with antimicrobial agents and to prevent complications of this condition on contrary to its counterpart Eumycetoma which is treated mostly by surgical treatment.

References

1. Zijlstra EE, Van de Sande WWJ, Welsh O, Mahgoub ES, Goodfellow M, Fahal AH. Mycetoma: a unique neglected tropical disease. Lancet Infect Dis. 2016;16(1):100–12. https://doi.org/10.1016/S1473-3099
2. Sharma P, Wankhade AB, Gaikwad U, Das P. Detection of slow growing Actinomadura species proved a key for management of mycetoma: A case report from Chhatisgarh. J Family Med Prim Care. 2020;9(7):3745–48. https://doi.org/10.4103/jfmpc.jfmpc_481_20
3. Palestine RF, Rogers RS 3rd. Diagnosis and treatment of mycetoma. J Am Acad Dermatol. 1982;6(1):107–11. https://doi.org/10.1016/s0190-9622
4. Relhan V, Mahajan K, Agarwal P, Garg VK. Mycetoma: An update. Indian J Dermatol. 2017;62:332–40. https://doi.org/10.4103/ijd.IJD_476_16
5. Rattanavong S, Vongthongchit S, Bounphamala K, Vongphakdy P, Gubler J, MayxayM,et al.Actinomycetoma in SE Asia: the first case from Laos and a review of the literature. BMC Infect Dis. 2012;12:349.https://doi.org/10.1186/1471-2334-12-349
6. Damle DK, Mahajan PM, Pradhan SN, Belgaukar VA, Gosavi AP, TolatSN,etal. Modified Welsh regimen: A promising therapy for actinomycetoma. J Drugs Dermatol. 2008;7:853–6. PMID: 19112799
7. Sampaio FM, Galhardo MC, Quintella LP, Souza PR, Coelho JM, Valle AC. Eumycetoma by Madurellamycetomatis with 30 years of evolution: a therapeutic challenge. An Bras Dermatol. 2013;88:82–4. https://doi.org/10.1590/abd1806-4841.20132136
8. Karrakchou B, Boubnane I, Senouci K, Hassam B. Madurellamycetomatis infection of the foot: a case report of a neglected tropical disease in a non-endemic region. BMC Dermatol. 2020;20(1):1. https://doi.org/10.1186/s12895-019-0097-1
9. Fahal A, Mahgoub ES, Hassan EAM, Jacoub AO, Hassan D. Head and neck mycetoma: the mycetoma research centre experience. PLoSNegl Trop Dis. 2015;9(3):e0003587. https://doi.org/10.1371/journal.pntd.0003587
10. Verma P, Jha A. Mycetoma: reviewing a neglected disease. Clin exp dermatol. 2019;44(2):123–29. https://doi.org/10.1111/ced.13642
11. Welsh O, Sauceda E, Gonzalez J, Ocampo J. Amikacin alone and in combination with trimethoprim-sulfamethoxazole in the treatment of actinomycotic mycetoma. J Am Acad Dermatol. 1987;17(3):443–8. https://doi.org/10.1016/s0190-9622(87)70227
12. Ramam M, Garg T, D'Souza P, Verma KK, Khaitan BK, Singh BK,et al. A two-step schedule for the treatment of actinomycotic mycetomas. Acta DermVenereol. 2000;80(5):378–80. https://doi.org/10.1080/000155500459367