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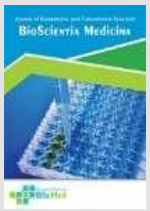

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Extensive Actinomycetoma Clinical Manifestations and Histopathology: A Case Report

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A B S T R A C T

Background: Actinomycetoma is a chronic infection of cutis, subcutaneous, bone, and viscera tissue. It is characterized by sinuses containing masses of causative organisms often referred to as "grains." Actinomycetoma is caused by aerobic bacteria, and they have been misclassified as a fungal species. Diagnosis of actinomycetoma was based on clinical features and confirmation by direct examination. This study aimed to describe the clinical and histopathological features of actinomycetoma. **Case presentation:** A 34-year-old woman complained of a mass on her left leg that had increased in number and pain 3 months before admission to the hospital with a history of trauma. Regio pedis sinistra has trias mycetoma, such as edema (swelling), multiple sinuses, and grain with hypertrophic scars. Histopathological with fibro collagenous connective tissue, moderate to dense diffuse PMN inflammatory cells, plasma cells, lymphocytes, hemosiderophages, multinucleated giant cells, epithelioid cells, and microorganisms. In periodic acid Schiff (PAS) there is the Splendore-Hoeppli phenomenon. **Conclusion:** Diagnosis of actynomycetoma was confirmed by the mycetoma triad and the Splendore-Hoeppli phenomenon. Actinomycetoma is more invasive and can cause bone destruction more quickly than eumycetoma.

1. Introduction

Mycetoma is a chronic local infection caused by fungal and bacterial species that invasion skin, subcutaneous tissue, bone, and viscera, although rarely. Mycetoma is caused by aerobic bacteria referred to as actinomycetoma or fungi as eumycetoma.[1–4] The most common organisms causing actinomycetoma worldwide are *Nocardia sp.*, *Streptomyces sp.*, and *Actinomadura sp.* These organisms enter the human body through direct contact with post-traumatic skin, so the most common predilection areas are the feet, lower legs, and hands. Actinomycetoma affects mainly men more than women, and the age ranges from 20 to 40 years old.[1-3] Actinomycetoma can occur in all parts of the world but is generally found in tropical and subtropical areas with low annual rainfall.[2]

Mycetoma can affect the skin, subcutaneous tissue, bone, and internal organs. It is characterized by swelling, deformation on the affected area, and fistulae that drain serosanguineous or purulent exudate.[4] A significant sign of a mycetoma is painless tumor-like swelling of subcutaneous tissue, also called tumefaction. Distinctive for both eumycetoma and actinomycetoma is the formation of grains. Grains represent microcolonies of the causative organism in

vivo in tissue.[5] Actinomycetoma can be distinguished by the characteristics of grain, and filament size on microscopic examination, histopathological appearance, culture, and risk of complications to underlying tissue.[2,6]

Diagnosis of actinomycetoma is suspected based on clinical features and confirmation by direct examination.[4] Differential diagnoses of mycetoma mainly include other subcutaneous infections with similar presentations. Cutaneous tuberculosis, especially gumma of the foot, represents the main differential diagnosis in an endemic country where tuberculosis still causes ravages. Other atypical mycobacteriosis, blastomycosis, soft tissue tumors, and chronic fistulized osteomyelitis can have the same clinical presentation, but the pathognomonic presence of grains rectifies the diagnosis. [7]

Garza et al. in northeast Mexico reported 31 actinomycetoma cases. The most common etiological agent was *N. brasiliensis* followed by *A. madurae* and *A. pelletieri*. Almost 50% had bone involvement.[8] Primary Actinomyces spp, infection of the lower extremity is very uncommon because of the endogenous habitat of the organism. It can cause destructive changes to both skin and soft tissue and progress deeper to involve bone. The cases can be complex to both diagnose and manage, particularly where tumefaction exists.[9]

The grains or microcolonies are predominantly found in the depth of the skin. Grains are groups of fungal hyphae surrounded by an amorphous substance. The first examination with H&E staining of the tissue sections, but special fungal staining techniques like PAS (Periodic-acid-Schiff) reaction and Grocott–Gomori silver staining show more details. Furthermore, actinomycetomas should be investigated by Gram staining.[5]

Treatment trials or prospective descriptions of outcomes for actinomycetoma should investigate treatment efficacy for the different members of Actinomycetales, particularly Nocardia spp., with short-term and long-term treatment courses.[10] Early diagnosis and treatment could avoid devastating outcomes such as bone destruction.[11] This case reports a rare case of actynomycetoma in a woman 34-year-old with swelling, sinus, and grain.

2. Case Presentation

A 34-year-old woman presented with 3 months history of soft tissue swelling with nodules on the left leg and pain. Around 8 months before there are multiple papules appeared on the left plantar pedis, painless, with no itching, and enlarged into nodules. It grows into a lump which then softens, the surface breaks, and releases a clear yellow liquid, sometimes accompanied by blood and yellowish-white granules (grain). New nodules then appear on both the back and soles of the feet, accompanied by swelling and pain. Two months before the rash appeared, the patient went to oil palm and rubber plantations several times. The patient does not remember that his left leg was injured or pierced by plant thorns. Patients always wear sandals when leaving the house, including while in the garden.

Pre-existing papules and nodules enlarge, soften, and partially rupture, releasing yellowish-white granules. The patient's feet begin to swell and painful. The patient went to an orthopedic specialist, and the patient's left leg was operated on because suspected to be cancer. Exploratory surgery, debridement, and biopsy of a nodule in the left plantar pedis are to be examined in pathology. The patient has been prescribed Levofloxacin 500 mg twice daily for 3 months, clindamycin 300 mg tablet 2 times daily for 3 months, and meloxicam 15 mg tablet once daily for 3 months. The drug is not consumed regularly. The patient was advised to control after 3 months of taking the drug, but the patient did not return to control with an orthopedic.

The patient went to a dermatologist for a physical examination. Status of dermatology dorsum pedis sinistra region, one-third left cruris distal: scar hypertrophic, solitary, hyperpigmented, linear, 10 cm x 0.3 cm x 0.2 cm. Eutrophic scars, multiple, hypopigmented, linear, 0.5 cm x 0.1 cm – 2 cm x 0.2 cm. *Dorsum, plantar, interdigital 2,3,4 pedis sinistra:*

edema, erythematous papules, multiple, lenticular to nummular, discrete, partially confluent. On the surface, there is a sinus with discharge in the form of a serous to serosanguinous exudate with yellowish-white grains and covered with yellow crusts, layered, and easily removed (Figure 1).

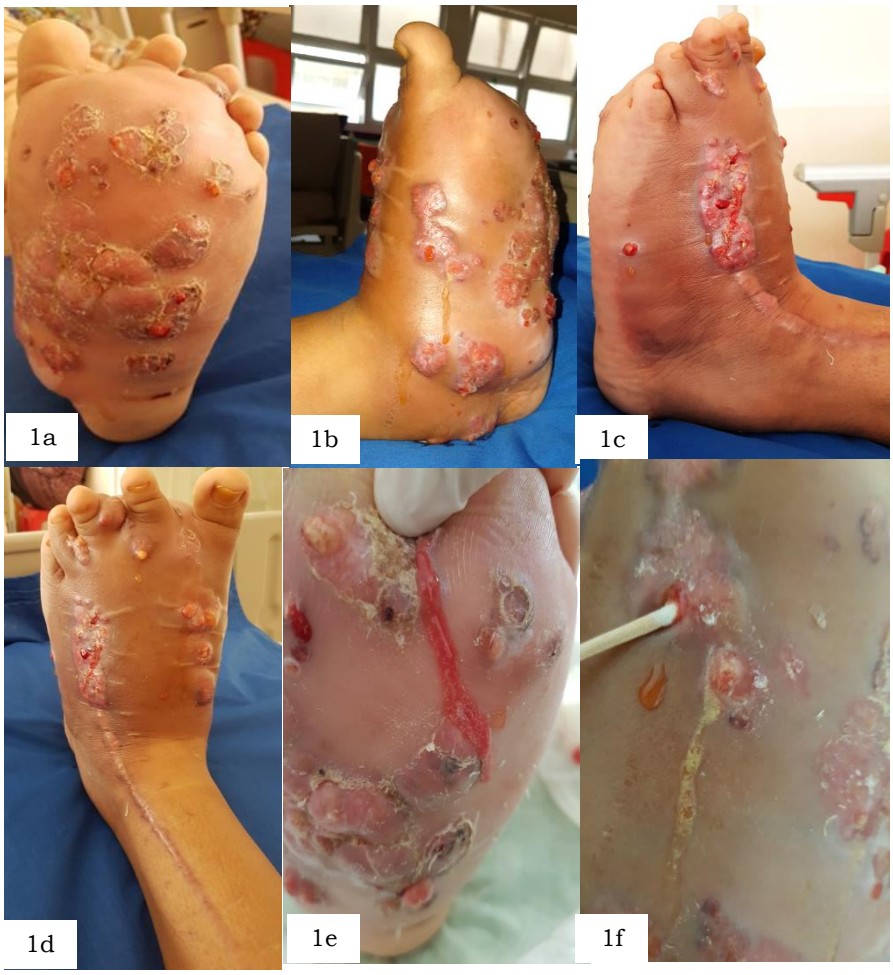

Figure 1. Region dorsum, plantar, interdigital 2,3,4: (a-d) Edema, erythematous with sinus and grains; (e and f) The surface contains sinuses with discharge in the form of serous to serosanguinous exudate with yellowish-white grains; (c and d) Region dorsum pedis sinistra, distal third of the left cruris.

The results of cultures and resistance test patients were resistant to Ampicillin, Cefotaxime, Ceftriaxone, Kanamycin, Sulfonamide, Chloramphenicol, Penicillin, and Erythromycin. History of frequent thirst, frequent hunger, frequent urination, and history of taking medication for diabetes was denied. The previous history of tumor or cancer was denied. A history of drastic weight loss, white tongue, and repeated diarrhea was denied. History of lung disease with long treatment was denied.

Histopathological examination with hematoxylin-eosin (HE) staining on tissue taken from medial nodule of medial plantar sinistra region found: fibro collagenous connective tissue, moderate to dense diffuse PMN inflammatory cells, plasma cells, lymphocytes, hemosiderophages, multinucleated giant cells, epithelioid cells, and microorganisms. Among

them were found an amorphous basophilic mass, fibroblast proliferation, and small blood vessels filled with red blood cells. In periodic acid schiff (PAS) painting, the Splendore-Hoeppli phenomenon was found (Figure 2). The conclusion of the biopsy results was actinomycetoma.

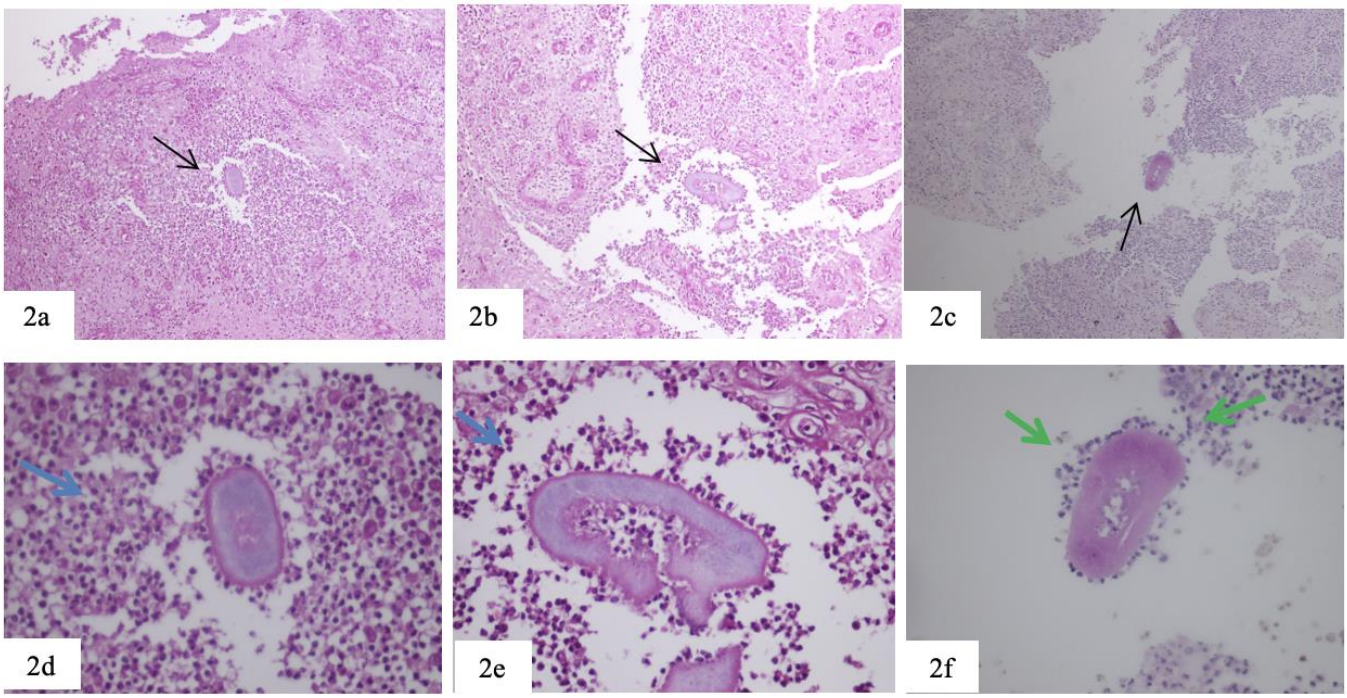

Figure 2**.** The histopathological picture with HE staining 100x (a and b) and 400x (d and e) upper dermis to lower dermis found suppurative granulomas (blue arrows) consisting of epithelioid cells histiocytes; PAS 100x (c) and 400x (e) in the suppurative area, the Splendore-Hoeppli phenomenon (green arrow).

3. Discussion

Mycetoma is one of the manifestations of deep subcutaneous fungal infection, chronic in nature, affecting skin, subcutaneous tissue, bone, and viscera, although it is very rare.[1,2] This disease often occurs in tropical and subtropical areas with low annual rainfall, sporadic even in tropical areas. Even endemic areas.[2] High incidence rates are found in countries that are included in the "mycetoma belt" which stretches between 15° south latitudes and 30° latitudes north of the equator, namely countries in Africa (Senegal, Sudan, Somalia), the Middle East (Saudi Arabia, Yemen), India, Pakistan, and South America (Mexico, Venezuela).[3,12] In developing countries, mycetoma mostly affects people who live in rural areas and work in the agricultural sector.[1,3,7] Mycetoma is more common in men than women, with a ratio of 4:1 and an age range of 20-40 years.[3] In this case, actynomycetoma in women 34 years old, although we know that actinomycetoma is common in men. This case came with Verdy et al. report case of actinomycetoma in women.[13]

Actinomycetoma is caused by aerobic bacteria, but because these bacteria produce filaments that resemble hyphae, these bacteria have long been misclassified as fungal species.[2] The most common causative organisms for actinomycetoma are *Nocardia sp.*, *Streptomyces sp.*, and *Actinomadura sp.*[3,12] The mechanism by which the mycetoma-causing organisms attack the host's defenses are not fully known, but it is thought that these organisms enter through skin trauma and adapt and survive in the host environment by producing certain proteins such as melanin or altering cell wall metabolism such as making the cell walls thicker.[3,12] Predilection of mycetoma, especially in the lower leg and the foot, as

the most commonly affected area. Walking and not wearing shoes is a risk factor for mycetoma.[1] Mycetoma could be prevented by improving living conditions and by regular use of shoes in rural populations.[4]

Once the causative organism enters the patient's body, the incubation period can occur from several weeks to months. Subcutaneous nodules begin to form slowly but progressively, soften and form sinuses.[3,6,14] In this case, the patient's first complaint was 8 months ago, without any history of previous trauma. However, two months before the appearance of skin lesions, the patient went to the plantation area. Patients more often wear sandals to travel, including when going to the garden. Predilection, in this case, is the left foot. Predilection, in this case, is the same in another case. Predilection mostly in the lower extremity.[11,13,15–17]

Triad manifestations of mycetomas are swelling, draining sinuses, and the presence of grains or also called granules or sclerotia. [3,6,14] In early infection, the lesion is a tender, painless nodule that spreads slowly with Papules and draining sinuses forming on the surface of the nodule. Sinuses formed secrete exudate and grains, which are aggregates of causative organisms, so that they can be used to determine the etiology of mycetoma. Exudate may be serous, serosanguinous, or seropurulent, whereas grains that emerge from sinuses vary in size, color, and consistency.[3,14] Some grains are visible only with a microscope up to 1-2 mm in diameter. The consistency of grains, in most cases, is soft.[2]

The organism causing mycetoma produces an anesthetic substance that prevents painful stimulus from arising. Pain can occur when the sinus tract opens to the surface of the skin when the disease has lasted a long time and has damaged nerves. Spread of infection beyond the area of infection is rare, although local lymphadenopathy may be present. Systemic symptoms are also rarely found because mycetoma has very little risk of hematogenous or lymphomatous spread unless there is a secondary bacterial infection that causes bone destruction.[3,14], In this case, the triad of mycetoma, such as the swelling presence of draining sinuses that expel grains, is fulfilled. From anamnesis, it was found there was a tender lump that was painless and spread slowly. The lump softened, and then a liquid mixed with blood came out with yellowish-white granules like fish eggs from inside the lump, so it can be concluded that draining sinuses that secreted grains were formed in an advanced phase. The patient did not complain or show constitutional symptoms. This case has the same manifestation in Gannass, the swelling had gradually increased in size over a few years, but it was painless and thus had not restricted him from continuing to farm until the lesion started to affect mobility.[9]

Investigations for mycetoma include direct microscopic examination of grains, histopathological examination of biopsy tissue, a culture of grains and/or tissues, histopathological examination of fine-needle aspiration, immuno-diagnosis, serodiagnosis, and molecular methods.[3] The difference between the organisms that cause eumycetoma and actinomycetoma lies in the size of the filaments. Eumycetoma has wider filaments with a diameter of 2-4 μm while actinomycetoma has finer filaments with a diameter of 1 μm or less. Direct microscopic examination of grain specimens can reveal differences between these two filaments. Gram-positive staining indicates actinomycetoma, and gram-negative indicates eumycetoma.[2,3]

Examination of grains with the addition of KOH did not allow to see fine filaments of actinomycetoma.[2] This simple grain examination could help in defining the nature of infection and choosing either antibacterial or antifungal treatment before the culture reports are obtained.[11] Histopathological examination revealed grains in the center of the zone of suppurative granulomas in subcutis. Neutrophil invasion is occasionally seen in grains. Around the area of suppuration can be seen rows of histiocytes above the inflammatory, infiltrate, and progressive fibrosis. In addition, several multinucleated giant cells can also be seen. The Splendore-Hoeppli phenomenon can be found around grains.[14,18]

Identification of the causative species can be determined by examining tissue cultures obtained from excisional biopsies, whereas the culture of grain specimens is not helpful because the causative organism is often invisible, and there is a risk of bacterial contamination.[2,3,14] Due to a large number of mycetoma-causing species, cultures need to be performed on several media and with different incubation methods.[2,14] Microorganisms can be cultured on media agar of Sabouraud's dextrose or Lowenstein-Jensen at room temperature.[1] In this case, a yellowish-white macroscopically visible grain was obtained. Histopathological examination with HE staining showed chronic inflammation of granulomatous-caused microorganisms. While the PAS staining obtained positive results with Splendore-Hoeppli to an impression of mycetoma. This case is the same with Verdy et al. histopathology with Splendore-Hoeppli.[13]

Actinomycetoma is treated with a combination of antibiotics, such as a combination of dapsone 100-200 mg/day with intramuscular (IM) streptomycin 1 g/day or trimethoprim-sulfamethoxazole (cotrimoxazole) 160/800 mg twice/day with rifampicin 300 mg twice/day or IM streptomycin 1 g/day.1 Amikacin IM 15 mg/kg/day or imipenem intravenous (IV) 1500 mg or a combination of both can be used for severe actinomycetoma or involving bone and viscera.[2,4,14] Clindamycin, ciprofloxacin, and moxifloxacin can be used in actinomycetoma caused by Nocardia. Mycetoma treatment can last a long time, namely months to years, especially if there are complications in the bone or viscera. The results of therapy vary depending on the cause.[2,14,19,] In this case, a combination of rifampicin 600 mg twice daily and cotrimoxazole 960 mg twice daily. The condition of the patient improved with a decrease in pain, swelling, amount of grain, and discharge. In this case, in some other cases that treatment with cotrimoxazole has been sufficient to cure the infection as defined by 43 weeks follow-up. Trials or prospective descriptions of the efficacy of different antimicrobial therapy with short-term and long-term treatment courses for actinomycetoma should investigate.[10]

The response therapy can be seen from clinical assessment, laboratory results such as hemoglobin, leukocyte, C-reactive protein (CRP) levels, biopsy results, and culture. Resolution declared if there are no clinical symptoms, no grains, and negative culture results.[1,19] The response of therapy in patients is good, with decreased leukocytes in the blood.

Surgery is an integral component of the diagnosis and management of mycetoma. As a treatment, surgery on mycetoma aims to reduce spread, get a better response to treatment, and is a life-saving measure in severe infection or sepsis. Surgical options for the management of mycetoma vary from debridement to amputation of the infected site to prevent spread and recurrence.[14] Surgical options for mycetoma treatment range from a wide local surgical excision to repetitive debridement excisions to amputation of the affected part. Adequate anesthesia, a bloodless field, wide local excision with adequate safety margins in a suitable surgical facility, and expert surgeons are mandatory to achieve the best surgical outcome. Surgical intervention in mycetoma is associated with considerable morbidity, deformities, and disabilities, particularly in advanced diseases.[20] In this case, the patient, must operate, but the patient rejects operated.

Actinomycetomas of a few months duration and without bone involvement respond well to therapy. If no therapy is provided or if there is resistance, the functional and cosmetic prognosis is poor, mainly for the feet.[4] Mycetoma may cause limb deformity, amputation, and even death if left untreated.[11] Prognosis of this patient is poor because have the complication of osteomyelitis.

4. Conclusion

Actinomycetoma is a type of mycetoma caused by a bacterial infection. Actinomycetoma spreads faster, the inflammatory reaction is more severe, suppurative, causes more sinus formation, and is invasive. Actinomycetoma caused bone destruction more

quickly than eumycetoma. The diagnosis can be confirmed by mycetoma triad and histopathology of the Splendore-Hoeppli phenomenon.

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