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Actinomycetoma by *Cellulosimicrobium cellulans* in a Young Man from Guinea-Bissau: Short Literature Review Regarding a Case Report

Actinomicetoma por *Cellulosimicrobium cellulans* num Jovem Guineense: Breve Revisão de Literatura a Propósito de um Caso Clínico

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ABSTRACT

Mycetoma is caused by the subcutaneous inoculation of filamentous fungi or aerobic filamentous bacteria. *Cellulosimicrobium cellulans* is a gram-positive bacterium from the order *Actinomycetales* that rarely causes human disease. The diagnosis is based on the clinical presentation and identification of the causative microorganism. We present a short literature review regarding the case report of a young man diagnosed with actinomycetoma due to *Cellulosimicrobium cellulans* and treated with an association of amikacin and sulfamethoxazole/ trimethoprim (Welsh regimen).
Keywords: Actinomycetales; Mycetoma/diagnosis; Mycetoma/therapy

RESUMO

O micetoma é causado pela inoculação subcutânea de fungos filamentosos ou bactérias filamentosas aeróbias. *Cellulosimicrobium cellulans* é uma bactéria Gram positivo da ordem *Actinomycetales*, que raramente causa doença em humanos. O diagnóstico é baseado na apresentação clínica e na identificação do microrganismo. Apresentamos uma breve revisão de literatura, a propósito do caso clínico de um jovem com diagnóstico de actinomicetoma por *Cellulosimicrobium cellulans* tratado com uma associação de amicacina e sulfametoxazol/trimetoprim (esquema de Welsh).
Palavras-chave: Actinomycetales; Micetoma/diagnóstico; Micetoma/tratamento

INTRODUCTION

Mycetoma is a chronic, localized and slowly progressive disease of the skin and soft tissue, caused by ubiquitous bacteria (actinomycetoma) and fungi (eumycetoma).[1] It is endemic in tropical and subtropical areas. The treatment depends on the etiology and other factors, and the cure rate is variable.[2–4] *Cellulosimicrobium cellulans* (*C. cellulans*) is a Gram-positive bacteria that rarely causes human disease.[5,6]

We present the case of a young man from Guinea-Bissau diagnosed with actinomycetoma due to *C. cellulans*. The indolent clinical course and complications, related to the delayed diagnosis and multiple therapeutic regimens, underline the importance of its recognition in non-endemic countries.

CLINICAL REPORT

In 2017, a 17-year-old male from Guinea-Bissau was transferred under an agreement between the governments of Portugal and Guinea-Bissau to a Paediatric Infectious Diseases department in Portugal, for the investigation of intermittent fever and nodular exudative lesions of the left foot that had been evolving for six years. With no history of trauma, he initially had a painless nodule on the plantar aspect of the foot that gradually developed purulent discharge and a firm swelling.

On physical examination, he had multiple infiltrative nodules and sinuses, with purulent and haemorrhagic drainage, and oedema reaching the ankle and leading to important functional limitations (Fig. 1). The Laboratory tests revealed a normal blood cell count, elevation of C-reactive protein (52.7 mg/L) and erythrocyte sedimentation rate (44 mm/h). The interferon-gamma release assay (IGRA) was negative and the chest X-ray was unremarkable. A magnetic resonance imaging (MRI) of the left foot revealed a granulomatous mass with extensive local involvement of the subcutaneous tissue, muscles, and bones, with multiple nodular lesions showing the 'dot-in-circle' sign and several foci of avascular necrosis of the bone (Fig. 2).

The histologic examination of a tissue biopsy identified spore aggregates with periodic acid-reactive Schiff (PAS) stain. Admitting the diagnosis of eumycetoma, he was started on itraconazole.

Due to lack of clinical improvement, a second biopsy was performed. The histological examination showed a "granulomatous inflammatory infiltrate and basophilic filamentous microorganisms suggestive of *Actinomyces*" and the pan-bacterial polymerase chain reaction (PCR) identified *C. cellulans*, thus supporting the diagnosis of actinomycetoma.

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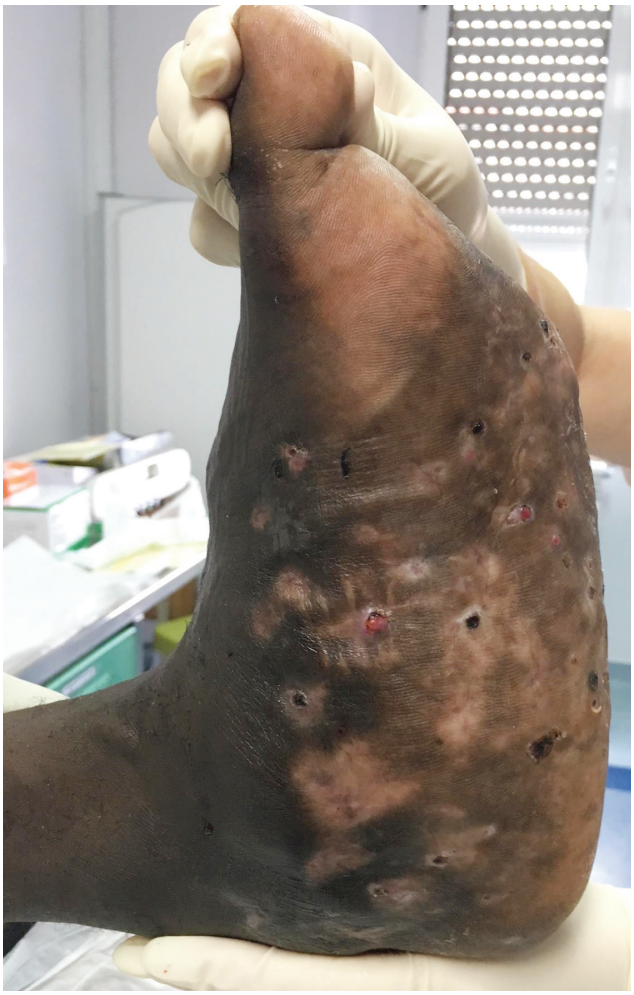

Figure 1 – Actinomycetoma of the left foot: multiple nodular lesions with sinuses and severe deformity

In the following months, the patient received sequential treatment with β-lactams, aminoglycosides and sulfamethoxazole/trimethoprim (STX/TMP) in monotherapy and underwent several surgical debridements, without improvement of the nodules and oedema.

In 2018, he received treatment with continuous oral STX/TMP in association with a four-week course of meropenem every two weeks, complemented by debridements and hyperbaric oxygen treatments.

In April 2019, the patient was transferred to the adult ID Department, with nine cycles of this regimen completed, showing regression of the oedema, but still with recurrence of the subcutaneous nodular lesions between meropenem courses. He was reassessed with an MRI, which, despite showing some improvement, identified multiple bone and subcutaneous lesions.

After a review of the literature, he was started on four courses of amikacin 15 mg/kg/day for three weeks and continuous oral STX/TMP 35 mg/kg/day, with two-week amikacin free periods.

The patient completed treatment, without relapse of the lesions after the second course of amikacin, and with full functional recovery. No otologic or renal toxicity occurred.

For the next 15 months, he was evaluated every three months, without recurrence of lesions on physical examination. In January 2021, the magnetic resonance imaging (MRI) showed significant decrease in the number of lesions, no new nodules and stable bone involvement (Fig. 3).

DISCUSSION

The first case of mycetoma was described by Dr John Gill, in the Indian town of Madura, in 1842, referring to the disease as Madura foot.[7,8] Since 2016, it is among the neglected tropical diseases according to the World Health Organization.[9]

Most cases occur in the 'Mycetoma Belt', which includes tropical and subtropical areas of Africa, Central and South America and Asia, particularly the Indian subcontinent. The true incidence and prevalence are unknown.[2,9–11] Some studies demonstrate a higher prevalence in men, while others show no difference between sexes.[1,10,12,13]

It is a chronic, localized and slowly progressive disease and most frequently affects feet and hands. It is characterized by painless subcutaneous granulomas, with sinuses draining pus, blood and grains, which results in destruction of structures and deformity.[2,4,7,14–16] Bone involvement may occur.[4,12,13,16,17]

Mycetoma is caused by ubiquitous fungi (eumycetoma) or filamentous bacteria (actinomycetoma), found in soil and plants of endemic countries, with more than 50 species identified.[2,3,12,14,15] It is most frequently caused by *Nocardia*, *Streptomyces,* and *Actinomadura*.[2,4,11,17] The disease evolves within weeks to years after skin trauma.[15–17]

The diagnosis is based on physical findings, biopsy or fine needle aspiration, and imaging. The identification of microorganisms can be made by histopathologic examination, culture and molecular techniques, and involvement of structures can be evaluated using radiography, ultrasonography, computed tomography scan, and MRI, with the last being more sensitive.[2,18] The 'dot-in-circle' sign, in ultrasound or MRI, is considered pathognomonic of musculoskeletal mycetoma.[18,19]

The differential diagnosis includes sporotrichosis, tuberculosis, osteomyelitis, coccidiomycosis, botryomycosis, other fungal infections, and neoplasms of the bone and soft tissues.[4,11]

The treatment choice depends on the causative agent, disease extension, and host factors. The combination of STX/TMP and amikacin, with or without rifampicin (Welsh regimen and modified Welsh regimen) showed good

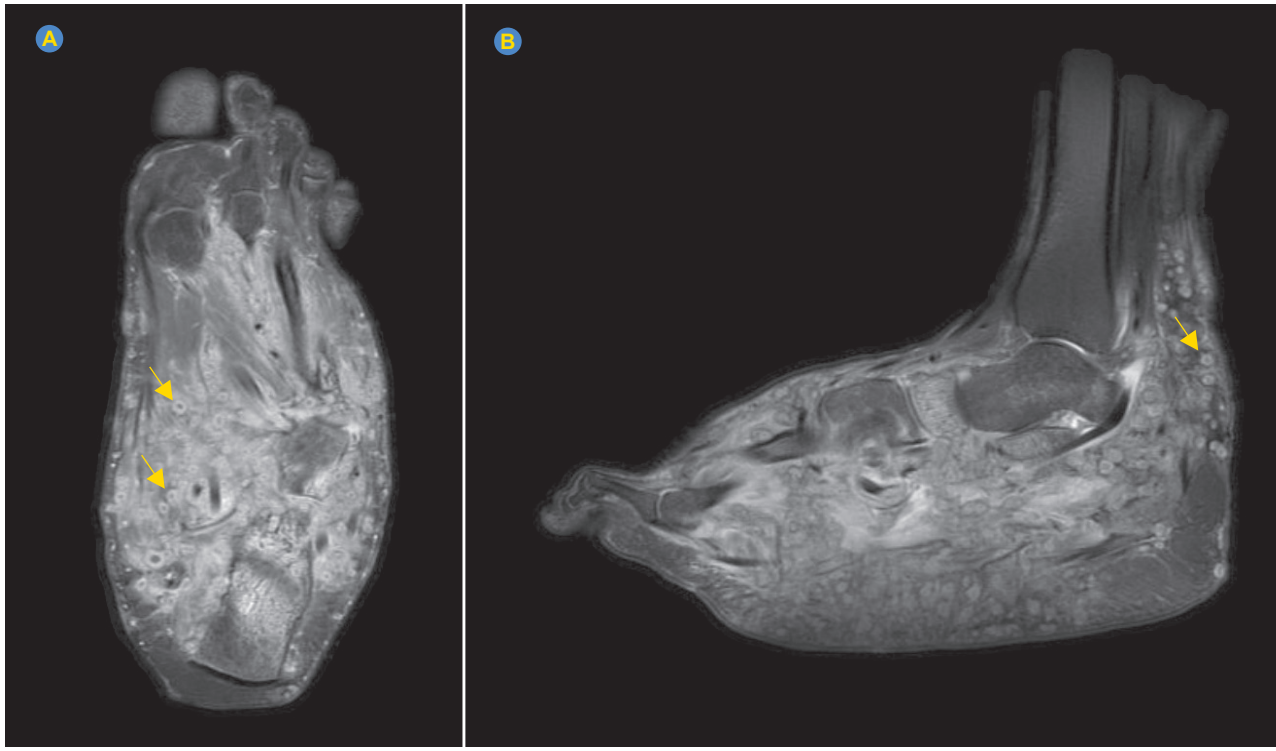

Figure 2 – MRI revealing nodular lesions, with 'dot-in-circle' sign (arrows), involving bone, muscles and subcutaneous tissue of the left foot

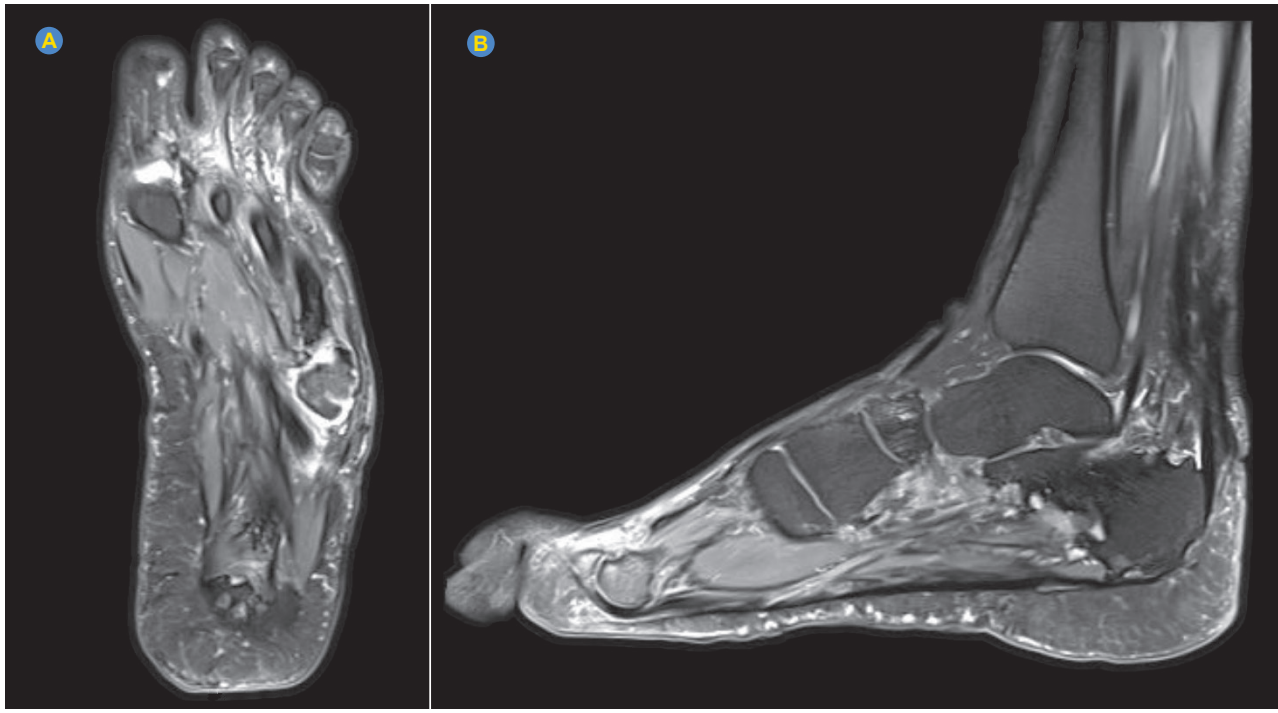

Figure 3 – Post-treatment MRI of the left foot showing regression of the lesions and tissue edema, with bone sequelae

outcomes.[11,13,16] The alternatives are STX/TMP and dapsone or rifampicin; amoxicillin/clavulanate and netilmicin, for STX/TMP and amikacin allergy, respectively; amikacin and meropenem or imipenem can be used in refractory cases; other combinations can be used as well.[4,12,13,15–17] The guidelines from the Mycetoma Research Centre of Khartoum recommend streptomycin and dapsone as first-line drugs.[20] Monotherapy is not recommended.[2,13,15,16]

Surgical treatment is indicated for localized lesions and for large lesions, in combination with antibiotics, to reduce the organism load.[17]

C. cellulans, formerly known as *Oerskovia xanthineolytica* and *Nocardia cellulans*, is a gram-positive bacillus from the order *Actinomycetales*, and is distributed widely in the environment. It is a rare human pathogen.[5,6]

In a literature review published in 2019, the main risk factors for *C. cellulans* infection were underlying chronic disease affecting the immune system and the presence of foreign bodies. Only one case of abscess formation related with intramuscular injections has been described. The isolates were susceptible to vancomycin, STX/TMP, imipenem and amikacin.[6]

The literature provides a good, albeit fragmented, overview of the presentation and etiology of mycetoma. However, there are no randomized controlled trials on the best therapeutic approach, leading clinicians to make decisions based on case reports, small retrospective studies, and scarce systematic reviews.

This case report describes a delayed and complex diagnosis of actinomycetoma, which happen often outside reference centres. Therefore, it emphasizes the importance of early recognition of the disease and identification of the causative microorganism.

Several factors may have contributed to the ineffectiveness of the previous therapeutic regimens, such as lesion extension, difficult identification of the microorganism and no antibiotic susceptibility testing, monotherapy regimen, and short courses of treatment.

The decision on the best therapeutic approach was also challenging due to lack of guidelines for the treatment of mycetoma in our setting and no information on the susceptibility profile of *C. cellulans.*

AUTHORS CONTRIBUTION

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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