Case Report

A TROPICAL DIABETIC FOOT

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ABSTRACT

Foot infections are a common problem and an important cause of morbidity in patients with diabetes. We report a patient with type 2 diabetes, presenting with a chronic foot wound resistant to standard care, in whom the diagnosis of eumycetoma was made through histopathological examination of a bone biopsy specimen and confirmed by polymerase chain reaction (PCR). Diagnosis and treatment of eumycetoma are reviewed. Eumycetoma caused by *Madurella mycetomatis* is an uncommon cause of osteomyelitis in patients with diabetes in Europe, but should be considered in patients from endemic regions when (antibacterial) therapy fails.

Key words: diabetic foot, fungal infection, therapy

INTRODUCTION

Foot infections are a common problem in patients with diabetes. They cause important morbidity and may lead to amputation of a lower limb, despite therapy. Therefore, they should be managed by a multidisciplinary foot-care team, preferably including an infectious diseases or microbiology specialist. Aerobic gram positive cocci are the most frequent cause of infection in diabetic foot. In chronic wounds, however, the infection tends to be polymicrobial, including gram negatives and anaerobes (1). The present case illustrates the need to identify the causative organism(s) in order to provide adequate therapy, especially when antibiotic-resistant or uncommon organisms may be involved.

CASE REPORT

A 52 year old Moroccan farmer, diagnosed with type 2 diabetes mellitus two years previously, presented to our hospital for a second opinion concerning painless chronic (more than 10 years) wounds at his right foot. In the past years, he had been treated with several topical therapies and oral antibiotics in his home country, without sustained improvement. An operation with amputation of the foot had been proposed to him on several occasions, but he had refused. The man was currently treated with oral antidiabetics, with excellent metabolic control. Other than diabetes, his medical history was unremarkable.

Physical examination on admission revealed several painless wounds at the dorsum of the right foot (figure 1 panel A): between the base of the first and the second toe and at the base of the third and the fourth toe, in the region overlying the first tarsometatarsal joint and under the external malleolus; some of the wounds draining pus on pressure (University of Texas classification Grade III-B). There was no cellulitis, no swelling of locoregional lymph nodes, lower limb peripheral pulses were present, cutaneous sensibility at the feet seemed reduced, and further clinical examination was unrevealing. Laboratory tests showed no inflammation, HIV testing and a Mantoux skin test were both negative, and a chest X-ray was within normal limits. X-ray of the foot showed an image of extensive osteomyelitis, with lytic bone lesions in the diaphysis of the 1st, 2nd and 3rd metatarsal, lateral os cuneiforme and the os cuboideum, deformity of the proximal diaphysis of the first metatarsal and diffuse soft tissue swelling. Magnetic resonance imaging (MRI) of the foot (figure 1 panel B) showed marked gadolinium enhancement and destruction of bones and joints at the distal tarsus (including the Lisfranc joint complex, the midtarsal joint and the Chopart joint complex) and in the surrounding soft tissue, with several collections fistulising towards the skin.

A bone biopsy specimen was taken at the first tarsometatarsal joint, and was sent for routine hematoxylin-eosin, Ziehl-Neelsen and periodic acid-Schiff (PAS) staining. Gram stain and Ziehl-Neelsen stain were both negative. The samples were inoculated on blood agar (bacterial culture), Löwenstein-Jensen medium (mycobacterial culture) and Sabouraud's dextrose agar, and incubated at a temperature of 37°C and 25°C respectively. All cultures were negative, even after a

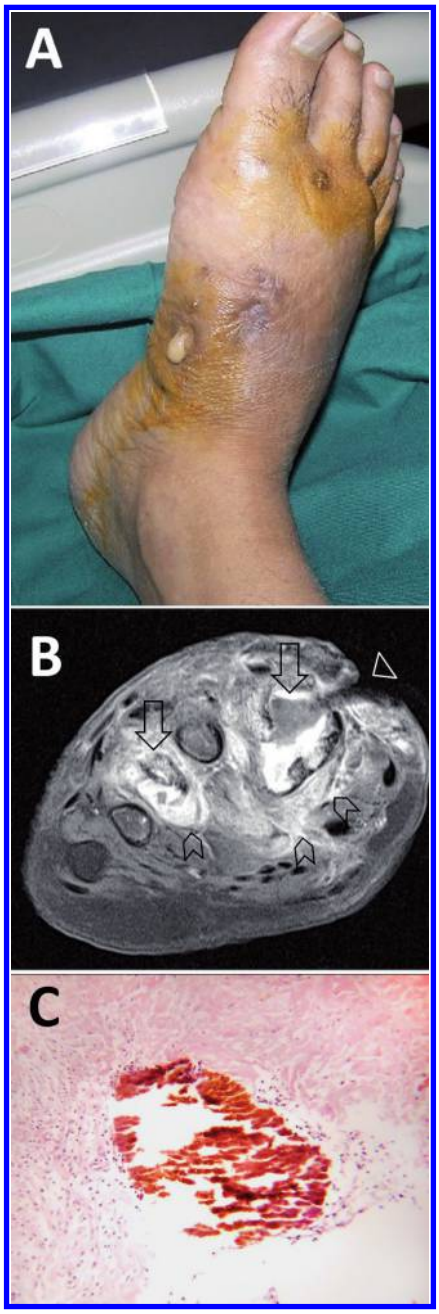

Figure 1: **A.** *View of the foot showing several suppurative wounds at the right foot of the patient.*
B. *T1-weighted short axis MRI image of the right foot with fat suppression technique after IV gadolinium DTPA administration (3 Tesla, Siemens Trio). Cross-section at the level of the metatarsals, including the base of the first metatarsal. White areas of enhancement (arrows) located at the first and third metatarsals show destruction; absence of enhancement at the central part of the first metatarsal corresponds with intraosseous abcedation. There is also enhancement at the peri-osseous soft tissues (arrowheads). Medial to the base of the first metatarsal, a deep skin defect (triangle) is visualised, with a sinus tract with connection to the cortical bone.*
C. *Histological examination of the bone biopsy specimen showing large grains (up to 5 mm) and interlacing hyphae, surrounded by polymorphonuclear and lymphocytic cells (PAS staining, magnification 10×).*

prolonged incubation time of three weeks, and eight weeks for the mycobacterial cultures. Histopathological examination of the bone biopsy specimens showed a chronic active inflammatory infiltrate with fibrin deposition. Although none were seen in the pus draining from the wounds, numerous black grains, typical for eumycotic mycetoma, could be distinguished in the biopsy material with the naked eye. Microscopically, some multinucleated giant cells were observed, and an important number of large amorphic structures corresponding with hyphae on a Period Acid Schiff stain (figure 1 panel C). As all fungal cultures remained negative, a Polymerase Chain Reaction of the Internally Transcribed Spacer (ITS-PCR) was performed on the remaining tissue. Direct sequencing of the obtained 500 bp PCR-product was shown to correspond for 100% with different strains of *Madurella mycetomatis* available in Genbank. The diagnosis of eumycetoma was made.

Since our patient had no pain nor disability from his wounds, it was decided to refrain from primary extensive surgery, and to start treatment with itraconazole 200 mg b.i.d., for a prolonged period of time . This therapy was both clinically and biochemically well tolerated and clinical evaluation after 6 weeks already showed a marked improvement with closure of all draining fistulas. The patient has now been followed for 15 months, and is (clinically, biochemically and radiographically) doing well under continued medical therapy. Regular MRI imaging of the foot may help to guide the duration of medical therapy and the timing of subsequent surgery, if required (2).

DISCUSSION

Mycetoma is a chronic granulomatous disease characterized by the formation of tumour-like masses. The aetiology is either fungal (eumycetoma) or bacterial (actinomycetoma). The fungus *Madurella mycetomatis* is the most common cause of eumycetoma worldwide, causing more than 70% of all mycetoma infections (3). The disease is endemic in tropical and subtropical regions (3), with reports of imported cases throughout the world. Eumycetoma is characterised by a triad of a subcutaneous mass with draining sinuses and the presence of grains. The causative organism is present in soil or plant materials. The infection is thought to start subcutaneously after minor penetrating injury, usually in labourers working barefoot in rural areas. Therefore, most cases are seen in males, and the site most involved are the feet (70%). Other predisposing factors are poor nutrition, poor hygiene, diabetes mellitus and immunosuppression. Eumycetoma is not self-limiting, but has a long incubation time and a prolonged and indolent course, with lesions extending to deeper tissues and bones, eventually leading to disability through deformity of the affected site.

Diagnosis of mycetoma in an endemic area is clinical, based on the presence of a subcutaneous mass, and the presence of sinuses and granular discharge. In the setting of imported pathology, as in this case, diagnosis may be delayed. The differential diagnosis of mycetoma includes classical bacterial infections and mycobacterial infection, but also soft tissue or bone tumours. Furthermore, differential diagnosis between bacterial or fungal causes of mycetoma is important

to provide an appropriate treatment. Unfortunately, differential diagnostic facilities are often restricted in regions where the disease is most prevalent (3).

Both direct examination of the grains and histopathological examination of the involved tissue appear to be useful to confirm the clinical suspicion of mycetoma, but are generally of limited use for the differentiation between different fungi (4). In our case, black grains were observed in the biopsy specimen. These are typical for eumycotic mycetoma, but although *Madurella mycetomatis* is the most frequent organism, black grains are also seen in occasional infection with *Leptosphaeria*, *Curvularia, Pyrenochaeta or Corynespora species* (3). Isolation and culture of the causative organism is difficult, even when deep surgical biopsies containing grains are used. After inoculation of the grains on Sabouraud's dextrose agar and incubation at 25 and 37°C, cultures become positive in only 20-50% of eumycetoma (4). It is therefore not entirely surprising that cultures remained negative in our patient. MRI is sensitive but cannot differentiate between fungal and bacterial causes of mycetoma, even in the presence of the rare 'dot-in-circle' sign, reflecting the fungal grains (a small hypointense focus or 'dot') in an inflammatory granuloma (high-intensity spherical lesions, or 'circle') (5). The sign was not present in our patient. According to literature, MRI is mainly used for follow-up, although the availability of MRI is limited in endemic areas. Available serological methods are low in sensitivity. Molecular tests, such as ITS-PCR (6), have been developed, allowing a better and faster identification of the causative organism. These may lead to better patient care and increased knowledge on disease epidemiology, but are not yet routinely used. In the present case, the diagnosis was strongly suspected after histopathological examination of the bone biopsy specimen, and confirmed by molecular techniques.

The management of eumycetoma includes antifungal therapy, preceded and/or followed by extensive surgery of the lesions, usually leading to permanent disability of the patient. A combination of medical treatment before and after surgery seems to result in the most successful outcome (2). Ketoconazole and itraconazole are recommended as first line agents in the treatment of eumycetoma, and treatment may have to be continued for up to 4 years (4), which makes cost of medical treatment and patient adherence a major issue. Itraconazole seems to have the highest success and lowest recurrence rate, with well encapsulated and more localised remaining lesions that are easier to resect (3). As there seems no longer any justification for mutilating surgery prior to medical treatment, our patient was started on itraconazole with careful and regular follow-up, in order to determine the need for and timing of surgery. Literature data on the ideal duration of follow-up of initially or purely medically treated eumycetoma do not exist, as in endemic countries, the disease is often advanced at diagnosis, requiring amputation.

In conclusion, mycetoma by *Madurella mycetomatis* is an uncommon cause of osteomyelitis in patients with diabetic foot in Europe, but should be considered in patients from endemic regions and when (antibacterial) therapy fails. Moreover, the condition may become more prevalent with increasing migration rates. This case illustrates that, in the absence of an adequate response to treatment, a deep tissue biopsy may be crucial for a correct diagnosis.

CONFLICT OF INTEREST: None.

ACKNOWLEDGEMENTS

The authors would like to thank prof. dr. K. Lagrou, (University Hospitals Gasthuisberg, Leuven, Belgium) for performing the molecular diagnostic procedure on the biopsy material.

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