THE MADURA FOOT : AN "INNOCENT FOOT MYCOSIS" ?

R. TEN BROEKE, G. WALENKAMP

With the increased movement of the world population, acquaintance with the clinical picture of the Madura foot is of growing importance beyond its original endemic areas. The characteristic triad of symptoms consists of indurated swelling, multiple sinus tracts with purulent discharge filled with grains and localization at the foot. An increasing number of new etiologic agents are recognized today. For a better choice of therapy an adequate diagnostic procedure is essential ; a deep biopsy for histology appears to give a more substantial contribution to identification of the causal organism than culture. The treatment which should be started early, is at first essentially a drug treatment. However, in spite of high expectations with regard to new antimycotic drugs, amputation or disarticulation is often inevitable even today, particularly when the lesion is caused by Eumycetes.

The first two documented patients with this disease in the Netherlands are described. They developed serious deformities of the lower extremity despite long-term use of antimycotic and antibiotic medication.

Keywords : Madura foot ; itraconazole-resistant *Phialophora cyanescens.*

Mots-clés : pied de Madura ; *Phialophora cyanescens* résistant à l'intraconazole.

INTRODUCTION

The Madura foot is a deep mycosis caused by exogenous fungal or actinomycotic agents which can lead to progressive infection of the skin, subcutaneous tissues, muscles and bone. After invasion of the organism, usually by saprophytic soil through local trauma of the foot, hand or (sometimes) the eyes, subcutaneous nodules develop containing suppurative granulomas and multiple cavities and sinus tracts discharging exsudate with grains, which in fact are colonies of the causal organism (12, 16).

Until recent years surgery was preferred as treatment of choice and in many cases amputation or disarticulation was required, particularly when the disease was caused by Eumycetes. With the introduction of new antimycotic drugs such as ketaconazole or itraconazole surgery is reserved exclusively for diagnostic procedures (7, 10, 13, 14).

In this article we describe two patients, one of whom showed an unusually protracted course of the disease caused by a micro-organism until then unknown and newly typified. After an initially favorable and promising therapeutic response to itraconazole, amputation was ultimately necessary after a follow-up of more than 20 years. The characteristic radiological presentation, macroscopic and microscopic features are discussed.

CASE REPORTS

A 71-year-old man, originally born in Indonesia and living in the Netherlands since 1950, presented for the first time to us in 1973 with complaints of painless swelling of his right foot for 15 years, with intermittent discharge of white-yellow grains from multiple sinuses (fig. 1). The history mentioned local trauma to the foot in 1948 in Java. Between 1950 and 1972 there were recurring small painless nodular skin lesions near the original

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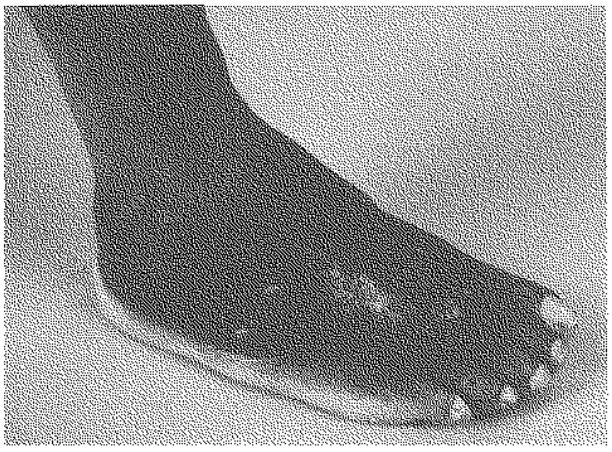
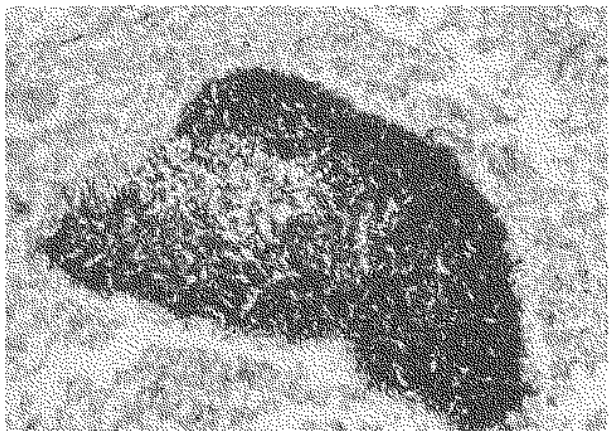


Fig. 1. — Macroscopic picture of mycetoma of the foot as described in our first patient.

wound which healed spontaneously, leaving minor scars. In 1973 laboratory findings and radiographs of the foot were (still) without abnormalities. Bacterial cultures taken of the suppurative discharge obtained from the sinus tracts were negative. Local excision was performed with primary closure of the defect. Histology showed an increase of fibrous connective tissue and an inflammatory polymorphonuclear reaction composed of granulocytes, plasma cells and histiocytes. In the center, grains were found (consisting of colonies of the causative agent) 0.5 to 1 mm in diameter, containing PAS-positive material. Branching hyphae with spores were detected (fig. 2). The picture was diagnosed as a "maduromycosis", but an exact identification of the fungus was not possible at that time.

In 1981 there was a relapse, and histopathology showed a similar picture. Cultures taken from a biopsy specimen showed a type of fungus not previously described in the literature nor identified as a cause of mycetoma. It was classified as *Phialophora cyanescens* (22) (Dr. G. A. de Vries, Central Bureau for Fungus Cultures, Baarn, The Netherlands) after consultation with leading international institutes of tropical medicine. The patient was treated with ketoconazole in a dose of 200 mg daily for 12 months. In 1983 this was repeated because of recurring symptoms. In 1987 radiographic bone manifestations were seen, including a periosteal reaction with lytic destruction in the spongiosa and cortical margin of metatarsal IV.

In spite of the regular use of ketoconazole there was an increase in infectious activity after 1990 with sclerosis and multiple cystic erosive lesions in several metatarsal bones, from which microscopy confirmed the earlier diagnosis (fig. 3). Because itraconazole, a newly registered antimycotic drug became available and sensitivity of the isolated fungus was proven *in vitro*, the previously planned amputation was cancelled and the clinical effect of the drug was awaited. Although the course of the disease was milder for several years, recent analysis revealed progressive bone destruc-



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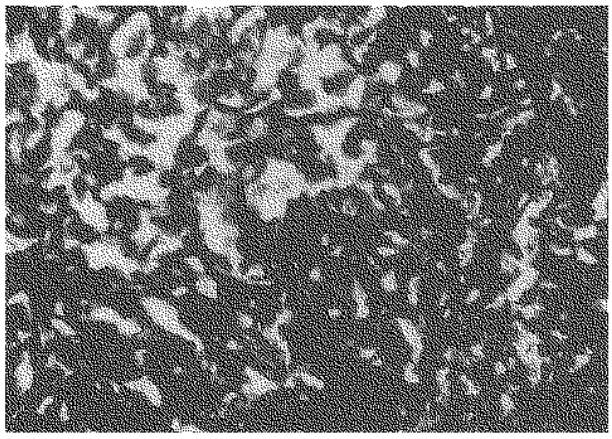

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Fig. 2. — Histology of a granuloma with a zone of polymorphonuclear granulocytes and centrally a characteristic grain with Grocott-stained material (a) × 125 with a detail of the hyphae (b) × 500.

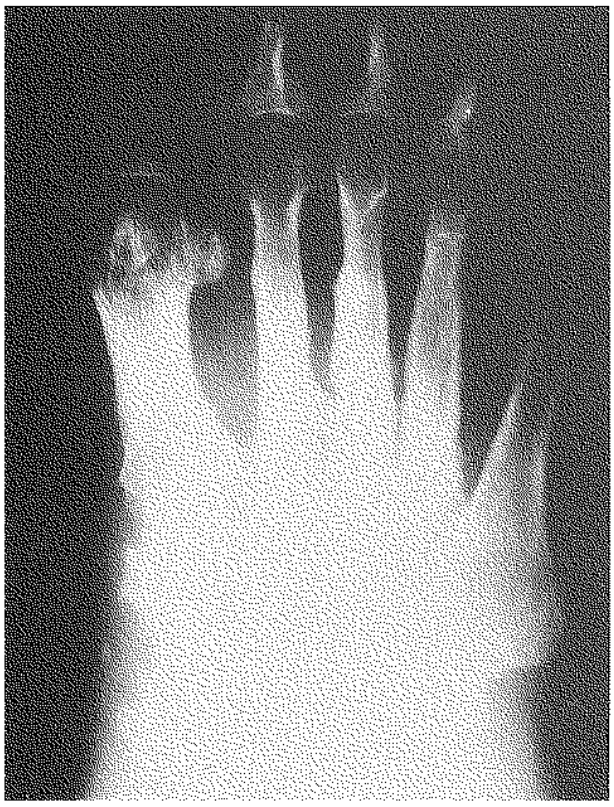

Fig. 3. — Radiograph showing multiple erosive defects in several metatarsals with periosteal reactions.

tion which by then affected the distal tibia and fibula as well (fig. 4). Increasing pain and disability without any response to intravenous amphotericin B ultimately necessitated amputation (fig. 5).

The second patient, a 36-year-old African man, sustained a bayonet injury of his left foot in 1985 during the conflict in Somalia. In 1993 he was seen with periodically draining sinuses of the foot. A regular radiograph and CT-scan showed multiple small cavities in the calcaneus, navicular and cuboid. Culture of biopsy material showed *Actinomadura madurae*, which was confirmed by the characteristic histology of the grains (fig. 6). Combination therapy with itraconazole with trimethoprim-sulfamethoxazole resulted in good clinical and radiological response after 3 months. Until now amputation has been avoided.

DISCUSSION

In 1842 the disease was recognized for the first time by Gill in the Madura district of India (5). Later, Bidie and Carter gave a full description of the disease (1, 2). Mycetomas are frequent in the tropical zones of America (Mexico and Venezuela), Africa (Senegal, Mauritania and Sudan) and Asia (India), but can also be observed beyond these areas.

Pseudallescheria boydii is most frequently seen in the USA (6), while *Madurella mycetomatis* and *Streptomyces somaliensis* predominate in tropical parts of Africa and India. *Nocardia brasiliensis* and *Actinomadura madurae* commonly cause mycetoma in Mexico and South America.

Fungi, that in these rainy areas are found as saprophytes in the soil, are usually introduced through skin wounds in those who walk bare footed (farmers, nomads) and are often exposed to penetrating wounds. Infection begins in the skin and subcutaneous tissue causing local papular or nodular swelling which tends to grow and rupture, forming communicating sinus tracts through which mucopus containing the characteristic colored grains is discharged. Some sinuses heal with scarring while fresh sinuses appear elsewhere, leading to enlargement and disfigurement of the affected limb (fig. 1). Eventually destruction of bone occurs when grains invade the cortical margins and replace the spongiosa (figs. 3, 4). General complaints are rare, and fever usually is a sign of secondary bacterial infection. The infection does not, in general, spread hematogenously although cases are known where particularly *Pseudallescheria boydii* and *Nocardia asteroides* in immunocompromised patients (leukemia, HIV, use of immunosuppressive drugs and prednisolone) have disseminated hematogenously to the brain, myocardium and thyroid (9, 23).

The combination of the clinical picture (indurated swelling of the foot with multiple sinuses that discharge pus filled with grains), macroscopically typical grains and the histopathology is characteristic of the diagnosis. Grains vary from 0.2 to 3.0 mm in diameter and can be black, white, yellow, pink or red, depending on the microor-

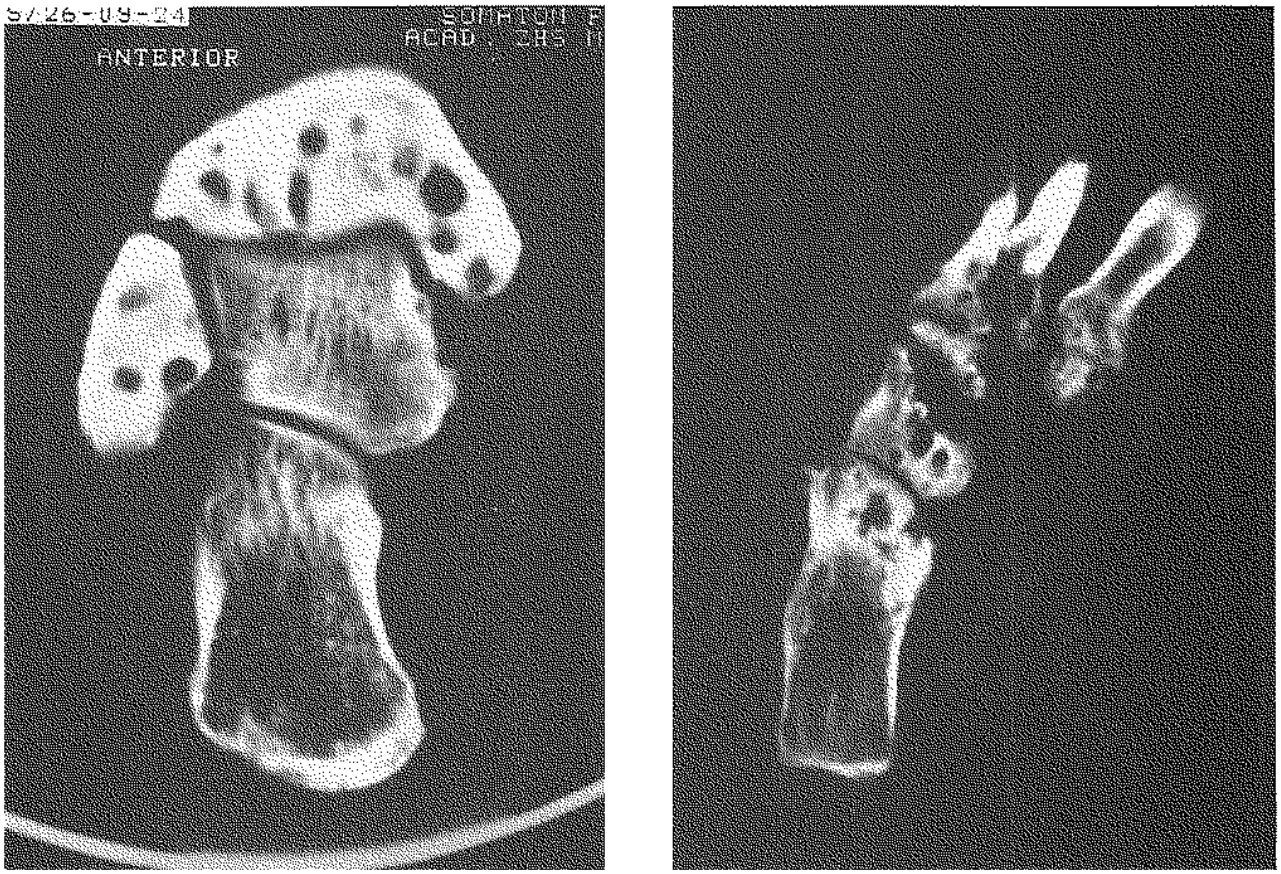

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Fig. 4. — CT-scan of the (a) ankle, frontal plane ; and (b) foot, coronal plane ; with osteolytic lesions in distal tibia, fibula and foot bones.

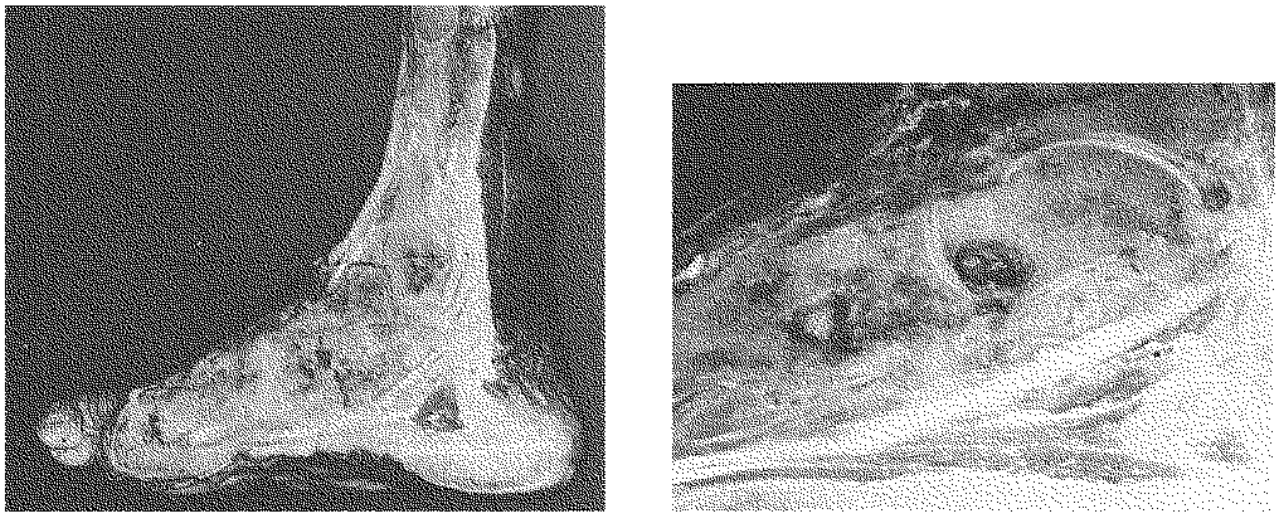

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Fig. 5. — Sagittal saw-cuts of the amputated lower leg with cystic bone destruction in distal tibia (a), talus and medial cuneiform bone detail (b) corresponding to the CT-picture.

Table I. — Etiology of mycetoma infections according to Mahgoub (4, 8, 9, 15, 20, 21, 22)

Eumycetoma	Actinomycetoma
Pseudallescheria boydii	*Actinomadura madurae*
Madurella mycetomatis	*Actinomadura pelletieri*
Madurella grisea	*Streptomyces somaliensis*
Phialophora jeanselmei	*Nocardia brasiliensis*
Pyrenochaeta romeroi	*Nocardia asteroides*
Leptosphaeria senegalensis	*Nocardia otitidiscaviarum (N. caviae)*
Curvalaria lunata	*(Nocardia transvalensis* (17))
Neotestudina rosatii	
Aspergillus nidulans of flavus	
Fusarium-species	
Cylindrocarpon	
Acremonium	

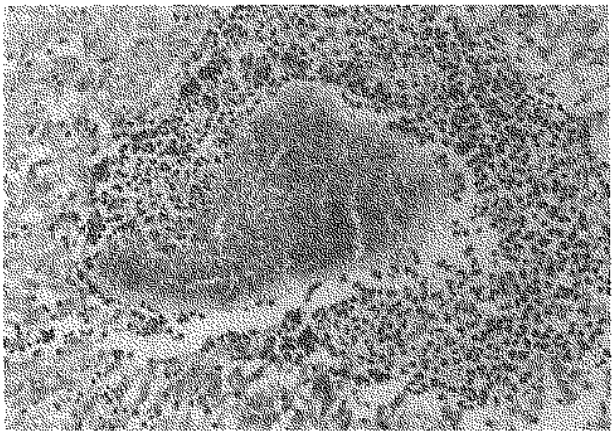

Fig. 6. — Hematoxylin-eosin stain of a grain of *A. madurae* with a polymorphonuclear inflammatory response, a dark-colored basophilic center and pale eosinophilic border ("Splendore-Hoeppli phenomenon") (× 125).

ganism (1, 15). On microscopy a hematoxylin-eosin (HE) stain will in general be able to demonstrate and identify the characteristic grains. They are surrounded by inflammation with neutrophilic polymorphonuclear and epithelioid cells, plasma cells and multinucleated giant cells with areas of fibrosis. Within these abscesses the basophilic grain is demarcated by eosinophilic hyaline-like material ; a combination known as the "Splendore-Hoeppli phenomenon" (26) (fig. 6). Two groups of mycetoma should be distinguished : "Eumycetoma" (caused by "eumycetes" or true fungi) and "Actinomycetoma" (caused by fungi-like aerobic bacteria from the *actinomycetes* species) (Table I). Since hitherto not described species of mycetes are mentioned such as *Phialophora cyanescens*, the list in this table cannot be considered complete (4, 8, 9, 15, 20, 21, 22). Although particular species of dermatophytes are known for their mycetoma-like infection as well, they do not lead to destruction of the bone and therefore are not considered real mycetoma (24, 25). Gram staining can be used for recognition of branching hyphae within the *actinomycetes* grains, while Grocott (= Gomori methenamine silver ; GMS) — or periodic acid Schiff (PAS) — staining is suitable for identification of the hyphae of eumycetes (fig. 2). Confirmation of the diagnosis and exact identification of the species require culture. Although theoretically more accurate than histology, culture is difficult practically. Grains discharged through sinuses can easily be contaminated, some fungi are very slow growing, and the advantage of histologic slides is that they are more easily sent for reappraisal than cultures. Serology may be helpful by demonstrating antibodies through immunodiffusion (precipitation) or electrophoresis against non-specific fungi.

Although the clinical picture is characteristic, diagnostic confusion may occur with chronic bacterial osteomyelitis, especially when bone destruction has occurred. Botryomycosis can give a similar picture ; it is a chronic bacterial infection

caused by gram-positive cocci (*Staphylococci, Streptococci*) and gram-negative bacteria (*Escherichia coli, Pseudomonas, Proteus*) that can lead to subcutaneous swelling with draining fistulas. Like mycetoma, grains (colonies of bacteria) can be found in suppurative discharge and biopsy specimens. In botryomycosis however organs can be affected by the process too. Neoplasms (benign and malignant) should be excluded as well (3).

It is essential that treatment be started at an early stage. For this purpose information campaigns for potential patients are crucial. Until some years ago differentiation between Eumycetes and Actinomycetes was considered essential, since there was no drug with proven efficacy for the first. Therefore until recently eumycetomas required surgical removal and showed a strong tendency to recur unless excision was adequate or amputation was high enough. Recent literature however suggests that all mycetomas may be amenable to medical treatment, particularly since the introduction of new azole-derivatives (7, 10, 13, 14, 18, 19). Despite long-term treatment with these antifungal agents in our first patient, drastic surgery could not ultimately be avoided. In cases of actinomycetomas a combination of two drugs is advised (11), one of which is always streptomycin (14 mg/kg daily for one month and on alternate days thereafter). In infections caused by *A. madurae*, dapsone (originally used in leprosy) is advised as a second drug (1.5 mg/kg twice a day). *S. somaliensis* can be treated with the same regimen or with trimethoprim-sulfamethoxazole (in divided doses of 4.6 mg/kg or 23 mg/kg daily respectively) instead of dapsone. Some *Nocardia* species appear to respond better to the combination of trimethoprim-sulfamethoxazole with dapsone or amikacin (15 mg/kg/day in 2 divided doses for 3 weeks) (7).

Several recorded eumycetomas appear to respond as well to administration of antifungal agents such as ketoconazole (twice a day 200 mg) and the relatively newer itraconazole (100 mg twice a day) (7, 10, 13, 14, 18, 19). Intravenous liposomal amphotericin B should only be considered as a second-line treatment because of its serious side-effects and only temporary remission. For most drugs it is recommended to continue treatment for at least 10 to 12 months with regular follow-up of hematologic parameters, liver and kidney functions.

REFERENCES

1. Bidie G. Notes on Morbus Pedis Entophyticus, Madras Quart. J. Med. Sci., 1862, 4, 222-227.
2. Carter H. On mycetoma or the fungus disease of India. London, Churchill, 1874.
3. Davies A. The bone changes of Madura foot, observations on Uganda Africans. Radiology, 1958, 70, 841-847.
4. Filipello-Marchisio V., Cassinelli C., Piscozzi A. *et al.* A preliminary survey of cycloheximideresistant airborne fungi in Turin, Italy. Mycopathologia, 1993, 123, 1-8.
5. Gill. India army medical reports. London, Churchill, 1874.
6. Green W., Adams T. Mycetoma in the United States. Am. J. Clin. Pathol., 1964, 42, 75-91.
7. Hay R., Mahgoub E., Leon G. *et al.* Mycetoma. J. Med. Vet. Mycol., 1992, 30, 41-49.
8. de Hoog G., Buiting A., Tan C. Diagnostic problems with imported cases of mycetoma in The Netherlands. Mycoses, 1993, 36, 81-87.
9. Juma A. *Phialophora richardsiae* endocarditis of aortic and mitral valves in a diabetic man with a porcine mitral valve. J. infect., 1993, 27, 173-175.
10. Mahgoub E., Gumaa S. Ketoconazole in the treatment of eumycetoma due to *Maduralla mycetomatis*. Trans. Ray Soc. Trop. Med. Hygiene, 1984, 78, 376-379.
11. Mahgoub E. Medical management of mycetoma. WHO Bull., 1976, 54, 303-310.
12. Mahgoub E., Murray I. G. Mycetoma. London, Heinemann, 1973, pp. 1-97.
13. Mahgoub E. Mycetoma. In : Jacobs P. H., Nall L., eds. Antifungal Drug Therapy. A Complete Guide for the Practitioner, New York, Marcel Dekker, 1990, pp. 61-70.
14. Mahgoub E. Mycetoma. In : Mahgoub E. S., ed. Tropical Mycoses, Beerse, Belgium, Janssen Research Council, 1989, pp. 57-74.
15. Mahgoub E. Agents of mycetoma, In : Mandell G. L., Bennett J. E., Dolin R., eds. Principles and Practice of Infectious Diseases, New York, Churchill Livingstone, 1995, pp. 2327-2330.
16. McGinnis M., Fader R. Mycetoma : A Contemporary Concept. Infect. Dis. Clin. North Am., 1988, 2, 939-954.
17. McNeil M., Brown J., Georghiou P. Infections due to *Nocardia transvalensis* : Clinical spectrum and antimicrobial therapy. Clin. Infect., 1992, 15, 453463.
18. Resnik B., Burdick A. Improvement of eumycetoma with itraconazole, J. Am. Acad. Dermatol., 1972, 33, 917-919.
19. Ruxin T., Steck W., Helm T., Bergfeld W., Bolwell B. *Pseudallescheria boydii* in an immunocompromised host.

Successful treatment with debridement and itraconazole. Arch. Dermatol., 1996, 132, 382-384.
20. Tomsikova A. Unusual causes of chromomycosis. Cesk. Epidemiol. Mikrobiol. Imunol., 1994, 43, 23-25.
21. Turiansky G., Benson P., Sperling L. *et al. Phialophora verrucosa* : A new cause of mycetoma. J. Am. Acad. Dermatol., 1995, 32, 311-315.
22. de Vries G., de Hoog G., de Bruyn H. *Phialophora cyanescens* sp. nov. with *Phaeosclera*-like synana morph, causing whitegrain mycetoma in man. Antonie van Leeuwenhoek, 1984, 50, pp. 149-153.
23. Welty F., Mc Leod G., Ezratty C. *et al. Pseudallescheria boydii* Endocarditis of the pulmonic valve in a liver transplant recipient. Clin. Infect. Dis., 1992, 15, 858-860.
24. West B. C. Five-year follow-up of a man with subcutaneous mycetomas caused by *Microsporum audouinii.* Am. J. Clin. Pathol., 1982, 77, 767.
25. West B., Kwon-Chung K. Mycetoma caused by *Microsporum audouinii.* First reported case. Am. J. Clin. Pathol., 1980, 73, 447-455.
26. Wethered D., Markey M., Hay R. Ultrastructural and immunogenic changes in the formation of mycetoma grains. J. Med. Vet. Mycol., 1987, 25,39-46.

SAMENVATTING

R. TEN BROEKE, G. WALENKAMP. De Madura-voet, een "onschuldige voetschimmel" ?

Door de toegenomen mondiale mobiliteit van de wereldpopulatie lijkt bekendheid met het beeld van de Madura-voet ook van toenemend belang buiten de oorspronkelijk endemische gebieden. De karakteristieke symptomentrias bestaat uit geïndureerde zwelling, multipele fistels welke met granulae gevulde pus draineren en de lokalisatie op de voet. Een groeiend aantal nieuwe micro-organismen wordt tegenwoordig herkend als oorzaak van deze aandoening. Voor een betere afstemming van de therapie is adequate diagnostiek essentiëel, waarbij een diepe biopsie ten behoeve van histologische identificatie van het causale micro-organisme zinvoller is dan een kweek. Behandeling dient vroegtijdig gestart te worden en met name medicamenteus te zijn. Ondanks hoge verwachtingen van nieuwe antimycotica, is echter ook tegenwoordig een amputatie of exarticulatie nog vaak geïndiceerd, met name in geval van Eumyceten. De auteurs beschrijven de eerste in Nederland gedocumenteerde patiënten met deze aandoening, bij wie ondanks langdurig gebruik van antimycotische en antibiotische medicamenten ernstige deformiteiten ontwikkelden.

RÉSUMÉ

R. TEN BROEKE, G. WALENKAMP. Le pied de Madura, une mycose «banale» ?

A cause de la mobilité croissante de la population mondiale, la connaissance du pied de Madura s'impose même en dehors des régions endémiques originales. La triade symptomatique caractéristique comprend une tuméfaction indurée, des fistules multiples qui donnent un pus granuleux et la localisation au pied. Actuellement un nombre croissant de nouveaux micro-organismes est reconnu comme responsables de cette lésion. Pour une meilleure sélection du traitement, un diagnostic adéquat est essentiel. La biopsie profonde, qui permet l'identification histologique du micro-organisme causal est préférable à une simple mise en culture. Le traitement doit être commencé tôt ; il est essentiellement médicamenteux. Malgré les espoirs qu'avaient suscités de nouveaux antimycotiques, une amputation est encore souvent indiquée, particulièrement en cas d'eumycétomes. Les auteurs décrivent les deux premiers malades documentés aux Pays-Bas ; malgré le recours prolongé aux antimycotiques et aux antibiotiques, tous deux ont présenté des lésions graves, qui ont imposé une amputation chez l'un d'entre eux.