Mycetoma (Madura Foot) in Israel: Recent Cases and a Systematic Review of the Literature

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Abstract. Mycetoma is a chronic soft tissue infection caused by fungal or bacterial pathogens, and is endemic in tropical and subtropical regions. Cases in developed countries outside the mycetoma belt are rare and usually imported by immigrants. Sporadic cases have been reported in Israel. Unpublished cases in the participating medical centers are reported. In addition, a systematic review of the literature was performed. All published mycetoma cases diagnosed in Israel were included with relevant variables collected. Twenty-one cases of mycetoma were diagnosed in Israel between 1942 and 2015, including four unpublished cases and 17 published cases. The mean age at diagnosis was 42 years (range 23–73), and 16 of the patients were male. The foot was the primary involved organ. Fifteen patients were immigrants from Yemen, Ethiopia, and Sudan. Five cases were autochthonous. One case was travel related. Among patients who developed symptoms after immigration, the mean time from exposure to symptom onset was 5.6 years (range 1–10 years). The mean time from symptom onset to diagnosis was 6.6 years (range 0.2–35 years). The autochthonous cases demonstrate that Israel is endemic of mycetoma. The immigrant population represents two distinct waves of immigration to Israel in the past century. Two unpublished cases of Ethiopian immigrants are the first reported cases of mycetoma acquired in Ethiopia. The diagnostic and therapeutic challenges along with the epidemiological data emphasize the need of raising the awareness of physicians to this devastating condition even in developed countries.

INTRODUCTION

Mycetoma is a chronic infection characterized by a triad of tumor-like swelling, multiple sinus formation, and a grain-containing discharge. This disease, recently defined by the World Health Organization as a neglected tropical disease, is burdening health systems worldwide, and its real impact is still thought to be highly underestimated.

“Madura foot” was first described in the south Indian city of Madurai by Gill in 1832,¹ for the unusual nodular appearance of the leg among field workers in the district. In 1860, it was named “mycetoma” by Carter who described its fungal etiology. Later, it was divided into two separate etiological categories—actinomycetoma (bacterial) and eumycetoma (fungal).² The most common causative agent of mycetoma worldwide is *Madurella mycetomatis*. The identification of the causative organism is crucial for guiding the treatment which differs greatly between the two groups of pathogens. Diagnosis is based on clinical characteristics, imaging, and microbiological identification of the organism. Imaging studies are also important for differentiating mycetoma from other subcutaneous masses, assessing the extent of the lesion, and possibly planning a surgical removal.

Most cases occur in the “mycetoma belt” which stretches between the latitudes of 15° south and 30° north, though cases have been reported beyond this area,³ usually in regions of hot and arid climates. Cases of mycetoma in developed countries are rare, usually imported by immigrants from endemic countries.⁴ Nevertheless, autochthonous cases in immunocompetent patients were also reported in developed countries,^{5–7} including the Mediterranean region.⁵

Mycetoma causes high morbidity. An early diagnosis and management of this rare infection are crucial in preventing disease progression, disability, and possibly even amputation.

In this report, we present four new cases of mycetoma and review the history of mycetoma infections reported in Israel. We thus aim to summarize the data, give some new insights, and raise the awareness of health-care personnel in non-endemic areas to this devastating condition.

METHODS

Unpublished cases of mycetoma from the authors’ medical centers were collected. In addition, a systematic review of the available literature on mycetoma cases in Israel was performed using the electronic database PubMed with the use of the following search terms: “mycetoma” or “madura foot” and “Israel.” The search was supplemented by reviewing the reference list of all relevant articles. All cases of mycetoma diagnosed in Israel and reported in the medical literature in all languages were included and all relevant variables were collected. Partial or full responses to treatment were documented based on the clinical data given.

RESULTS

The initial search yielded 24 articles, 16 of which were excluded by title and abstract evaluation. The full text of the remaining eight articles was assessed along with their references list (65 references), and six additional relevant articles were found. The full text of these articles was then also assessed with their references list (56 articles), yielding no additional articles. Altogether, of the 138 titles reviewed, 14 relevant articles were found using this search strategy, reporting 17 cases of mycetoma diagnosed in Israel. One more article describing a surgical procedure on a previously described patient was found randomly, resulting in a total of 15 articles.

In addition, we present four new cases which have not been published yet.

Case 1. A 23-year-old woman of Israeli–Arabic origin, who lived in an urban environment with no history of travel

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to endemic areas, presented with a 6-month history of swelling of her left foot. On examination, there was a 5 × 3-cm mass on the distal aspect of the left foot spreading to the second and third toes (Figure 1). A deep tissue biopsy was performed and a microbiological culture demonstrated *Nocardia caviae*. Triple therapy with monthly cycles of intravenous amikacin (for two consecutive weeks each month), oral rifampicin, and trimethoprim–sulfamethoxazole was initiated. The patient recovered completely after four cycles.

Case 2. A 40-year-old Israeli-born man of Yemenite origin presented with a 10-year history of progressive swelling and discharge from his right foot. He had no history of travel to endemic areas or occupational exposure. The patient received a few courses of antibiotics during this period but no diagnosis was made, and he was already unable to step on the affected foot. Discharge of white grains from multiple sinuses was apparent on the medial aspect of the foot. A deep tissue biopsy was performed and a diagnosis of *Actinomyces madurae* was eventually made in an Actinomycete reference laboratory, based on a tissue culture. This patient also received 6 months of triple therapy followed by trimethoprim–sulfamethoxazole monotherapy for an additional 1.5 years, after which he recovered completely.

Case 3. A 44-year-old woman of north Ethiopian origin who immigrated to Israel in 2002, presented in 2009 with complaints of swelling and pain in the right foot that started 3 years before her presentation and had progressed to a small tumor-like mass. She underwent surgical removal of the mass, during which black grains were apparent. Pathology demonstrated periodic acid Schiff–positive fungal spores and hyphae (Figure 2). Mycological cultures from the specimen were sterile. Pan-fungal polymerase chain reaction (PCR) was performed (according to the protocol described in

FIGURE 2. Pathological specimen from a foot infected with *Madurella pseudomycetomatis* mycetoma (case 3), demonstrating periodic acid Schiff–positive fungal spores and hyphae.

<http://sites.biology.duke.edu/fungi/mycolab/primers.htm>) and was positive for *Madurella pseudomycetomatis*. Treatment was initiated with itraconazole and the symptoms resolved for 1 year. Later, discontinuation of itraconazole treatment due to side effects led to disease progression with the formation of a sinus secreting black discharge. The patient underwent several surgical debridements combined with intermittent itraconazole treatment and has suffered from periods of relapsing and remitting disease since then.

Case 4. A 56-year-old man from northern Ethiopia presented with a 2-year history of soft tissue swelling and serous discharge from multiple secreting sinuses in his left ankle. These complaints started before his immigration to Israel while still in Ethiopia where he had worked as a farmer, usually walking barefoot in his fields. He did not recall any specific injury prior to developing these symptoms. He received a few courses of antibiotics while still in Ethiopia.

His physical examination revealed swelling, tenderness, and a serous discharge from multiple sinuses on both aspects of his left ankle (Figure 3). No grains were seen. A needle biopsy from the calcaneus was performed and the specimen was sent to pathology, direct microscopic smears, cultures, and a pan-fungal and pan-bacterial PCR. Though the direct smears and cultures were negative, results from the pan-bacterial PCR (16S rRNA gene PCR and

FIGURE 1. Foot of 23-year-old woman infected with *Nocardia caviae* mycetoma (case 1).

FIGURE 3. Left ankle of a 56-year-old man suffering from *Nocardia transvalensis* mycetoma (case 4), demonstrating swelling and multiple secreting sinuses.

sequencing) revealed *Nocardia transvalensis*. Treatment with high-dose trimethoprim-sulfamethoxazole was initiated with a good clinical response as seen with repeat examination and computed tomography after 3 and 6 months. However, the chronic infection and disuse of the foot and ankle have caused substantial atrophy and deformity of the involved area and the patient still suffers from a mild walking disability. Antibiotic treatment was stopped after 1 year of treatment, with no recurrence after 6 months of follow-up.

Review of literature. With the four new cases we presented, there are a total number of 21 cases of mycetoma diagnosed in Israel from 1942 to 2015. All cases are summarized in Tables 1 and 2.^{8–22}

There is a clear predominance of male gender in this series (16/21 patients, 76%). The mean age at diagnosis is 42 years (range 23–73). Of the 21 patients, 16 (76%) were immigrants, representing two waves of immigration to Israel. Of the first 12 consecutive patients in this series, 11 were immigrants who acquired the disease in Yemen.^{8–12,14,15} One patient,¹³ an immigrant from Iraq, and four Israeli-born patients^{16–18} were autochthonous cases. One travel-related case¹⁹ was documented in an Israeli-born patient, a returning traveler from southeast Asia. The latest four patients in the series²⁰ represent a second wave of immigration, from Ethiopia and Sudan.

All but one of the patients (95%) had a foot as the affected organ; one patient had suffered from an infection of the arm. Ten distinct pathogens are represented in our series, seven fungal (all but two are *Madurella* species) and 13 bacterial (six *Nocardia*, four *Actinomyces*, and three *Streptomyces* species). In one case, no final microbiological diagnosis was reached; we consider this case to be a probable rather than a definite case. The mean time from the last possible exposure to onset of symptoms in the five patients for whom we have this information was 5.6 years (range 1–10 years) and the mean time from symptom onset to diag-

nosis for all patients was 6.6 years (range 0.2–35 years). Of the 20 patients who received treatment, no response or a partial response to treatment was observed in seven patients (35%), whereas 12 patients recovered or showed a significant response to treatment with marked improvement (60%). One patient (5%) underwent complete amputation. One patient refused treatment and was lost to follow up.¹⁴ The patients who responded to treatment were more likely to suffer from actinomycosis compared with the patients who had partial or no response, but this difference was not statistically significant (data not shown). Five patients required surgical intervention; all of them suffered from a fungal infection.

A comparison between the two distinct immigrant groups in this series shows that patients of Yemenite origin had higher rates of actinomycosis (80% versus 25%, $P = 0.57$), longer mean time to diagnosis (10 years versus 2.4 years, $P = 0.15$), and higher non/partial response rates (44% versus 25%, $P = 0.55$) compared with patients from African origin, though none of these differences reached statistical significance.

DISCUSSION

Though mycetoma was first described in modern day India in 1832, it is considered to be an ancient disease in this region as presumably described by the ancient Sanskrit text *Atharva Veda* which refers to “Pada Valmikam,” meaning “anthill foot.”¹ There are modern reports of locally acquired cases also in temperate zones, mainly in southern Europe.⁵ It might very well be an ancient disease in the Mediterranean region as well, previously assumed to be the disease of Philoctetes, the mythological Greek hero described by the Greek tragedian Sophocles.^{23,24}

The recorded history of mycetoma in Israel may start as early as the byzantine period (300–600 AD). A female skeleton

TABLE 1
Mycetoma cases diagnosed in Israel: demographics and epidemiology

	Reference	Year*	Age (years)	Place of birth	Status	M/F	Acquisition	Time: last possible exposure to symptoms	Time: symptoms to diagnosis
1	Current	2014	56	Ethiopia	Immigrant	M	Ethiopia	Symptoms started in endemic area	2 years
2	Current	2009	44	Ethiopia	Immigrant	F	Ethiopia	4 years	3 years
3	Current	2005	40	Israel	Autochthonous	M	Israel	Unknown	10 years
4	Current	1990	23	Israel	Autochthonous	F	Israel	Unknown	6 months
5	20	2015	32	Sudan	Immigrant	M	Sudan	Symptoms started in endemic area	5 years
6	20	2015	23	Sudan	Immigrant	M	Sudan	Symptoms started in endemic area	2 years
7	19	1999	45	Israel	Returning traveler	M	Southeast Asia†	Symptoms started in endemic area	1 year
8	17, 18	1992	28	Israel	Autochthonous	M	Israel	Not specified	2 years
9	16	1988	43	Unspecified	Autochthonous	M	Israel	Not specified	2 months
10	15	1986	39	Yemen	Immigrant/ Autochthonous	F	Yemen	10 years	5 years
11	14	1986	67	Yemen	Immigrant	M	Yemen	Symptoms started in endemic area	30 years
12	14	1984	73	Yemen	Immigrant	F	Yemen	Symptoms started in endemic area	35 years
13	13	1980	41	Iraq	Autochthonous	M	Israel	Not specified	2 years
14	12	1960	55	Yemen	Immigrant	M	Yemen	Symptoms started in endemic area	10 years
15	12	1956	48	Yemen	Immigrant	M	Yemen	Symptoms started in endemic area	7 years
16	11	1956	35	Yemen	Immigrant	M	Yemen	Symptoms started in endemic area	10 years
17	11	1956	36	Yemen	Immigrant	M	Yemen	9 years	6 months
18	11	1956	44	Yemen	Immigrant	F	Yemen	1 year	4 years
19	11	1956	45	Yemen	Immigrant	M	Yemen	Symptoms started in endemic area	6 years
20	10	1952	24	Yemen	Immigrant	M	Yemen	Not specified	2.5 years
21	8, 9	1942	32	Yemen	Immigrant	M	Yemen	4 years	6 months

F = female; M = male.

*Year of diagnosis if specified or year of publication.

†History of travel to Indonesia, India, Thailand, Nepal, and Myanmar.

TABLE 2
Mycetoma cases diagnosed in Israel: pathogens, treatment, and outcome

Reference	Pathogen*	Treatment	Treatment duration	Outcome	Comment
1 Current	<i>Nocardia transvalensis</i>	TMP-SMX	1 year	R	
2 Current	<i>Madurella pseudomycetomatis</i>	Itraconazole, surgery	> 1 year and then intermittently	P	Few relapses during 6 years of intermittent therapy
3 Current	<i>Actinomadura madurae</i>	Amikacin, rifampicin, TMP-SMX	1 year	R	
4 Current	<i>Nocardia caviae</i>	Amikacin, rifampicin, TMP-SMX	1 year	R	
5 20	<i>Madurella mycetomatis</i>	Itraconazole	6 months	P	LFU
6 20	<i>Madurella mycetomatis</i>	Itraconazole	> 1 year	R	
7 19	<i>Cylindrocarpus lichenicola</i>	Surgery, amphotericin B, itraconazole	5 months	R	Surgical debridement and reconstruction
8 17, 18	<i>Madurella mycetomatis</i>	Ketoconazole, surgery	> 2 years	R	
9 16	<i>Actinomadura madurae</i>	TMP-SMX	7 months	R	
10 15	<i>Nocardia caviae</i>	Isoniazid, tetracycline, amikacin, rifampicin, TMP-SMX	> 1 year	R	Additional information obtained from the patient's physician
11 14	<i>Nocardia brasiliensis</i>	None	None	Unknown	LFU
12 14	<i>Nocardia brasiliensis</i>	Tetracycline	> 15 months	P	
13 13	<i>Nocardia caviae</i>	Surgery, isoniazid, TMP-SMX	> 1 year	R	
14 12	<i>Streptomyces madurae</i>	Streptomycin	2 months	P	Treated partially and LFU. Ten years later treated with streptomycin for 4 months with partial improvement.
15 12	<i>Streptomyces somaliensis</i>	Streptomycin	4 months	P	Recurrence 14 years after initial treatment. Treated again with streptomycin.
16 11	<i>Actinomadura madurae</i>	Streptomycin	6 months	R	
17 11	<i>Actinomadura madurae</i>	Streptomycin	2 months	R	
18 11	Unknown	Streptomycin	2 months	P	
19 11	<i>Streptomyces somaliensis</i>	Streptomycin, tetracycline	5 months	R	
20 10	<i>Madurella</i> species	Sulfadiazine, radiotherapy, surgery	1 month	R	Wide surgical debridement
21 8, 9	<i>Madurella</i> species	Sulfadiazine, radiotherapy, surgery	6 months	Amputation	

LFU = lost to follow up; P = partial response to treatment; R = significant response to treatment or full recovery; TMP-SMX = trimetoprim-sulfamethoxazole.

*As specified by the authors.

found in a byzantine era burial cave in the Bet Govrin area and reported by Herskovitz and others in 1992,²⁵ was found to have characteristic pathological changes in its lower extremities presumed by the reporters to be the result of a mycetoma infection. Since these were the only such findings in a large collection of skeletons from the region, the reporters hypothesized that the woman was not infected locally and might have been an immigrant from an endemic area. Though this theory was later challenged and an alternative diagnosis of leprosy was offered based on suggestive DNA results,²⁶ the diagnosis of mycetoma either as a primary or a secondary infection still holds substantial ground.

Almost all patients in this series were immigrants who acquired the disease in an endemic area. Looking into the demographics of these patients sheds light not only on the history of mycetoma in Israel, but also on some of the immigration patterns of this region in the last 100 years. The 11 patients of Yemenite origin and the four patients of African origin (Ethiopia and Sudan) represent two different immigration waves to Israel.

The first immigration wave represented in this series is of Yemenite Jews. Members of this ancient community started immigrating to Palestine at the turn of the 19th century, and the remainder of the community in Yemen and the British colony of Aden were airlifted to Israel after its foundation. Mycetoma in Yemen was first documented in 1906 by Frank G. Clemow, a British physician who published an

account of 10 cases in the *British Medical Journal*.²⁷ This disease is still prevalent in Yemen today as shown by two modern reports.^{28,29} Indeed, the first report of mycetoma in Israel was of a Yemenite Jew, published in 1942.⁸ The reporters suggested this may have been an autochthonous case, considering the reports of mycetoma from Middle East and Mediterranean countries. However, the discovery of 10 more mycetoma cases in subsequent years exclusively among Yemenite-born Jews strongly implies this disease was contracted in Yemen and imported to Israel. It is worthy to note another immigration wave from an area endemic to mycetoma to Israel that took place roughly around the same period. Members of a few distinct Jewish communities along the western coast of India (mostly Kochi and Bombay) immigrated to Israel in the 1950s–1960s. In contrast to the Yemenite immigrants, there were no reports of mycetoma among this group. Possible explanations to this may be 1) the fact that this region of India is less endemic than other areas in the subcontinent,³⁰ 2) the smaller size of this group, and 3) Indian immigrants mostly originated from urban areas and were less likely to be field laborers, probably reducing the risk of exposure to the common pathogens.

The second immigration wave from an endemic area that is represented in this series is of immigrants from Ethiopia and asylum seekers from Sudan and Eritrea. Ethiopian Jews started immigrating to Israel in the 1970s. There are an estimated 85,000 Ethiopian-born Jews living in Israel

today.³¹ Approximately 51,000 Sudanese and Eritrean nationals crossed the Israeli border since 2007 through the Sinai Peninsula in Egypt, escaping their countries and seeking temporary asylum in Israel. Around 40,000 remain in Israel today,³² following actions of the Israeli government to carry out repatriation and deportations of Sudanese and Eritrean asylum seekers. As mycetoma is highly endemic in Sudan, the two recently published cases of Sudanese patients²⁰ reflect the relatively high prevalence in Sudan. Conversely, the two unpublished cases of Ethiopian immigrants are to the best of our knowledge the first reported cases of mycetoma acquired in Ethiopia. Both patients are from the Gondar region in northern Ethiopia, a high altitude area with a temperate climate and periods of heavy rainfall in the summer. Although this region lies within the mycetoma belt, one could argue that this specific climatic area is not typical of mycetomas. Nevertheless, other areas in Ethiopia are of lower altitude and more arid conditions that are climatically similar to neighboring Sudan, Somalia, and Djibouti, all of which have numerous reports of mycetoma.³⁰ Thus, we presume that the lack of reports from Ethiopia lies not only in climatic and geographical differences but also in underreporting and underdiagnosis in this region.

Interestingly, 80% of patients of Yemenite origin in our series suffered from actinomycetoma infections. This is a contrast to the two latest reports of mycetoma in Yemen^{28,29} encompassing 85 patients, which demonstrated microbiological patterns similar to those seen in the neighboring region of east Africa, namely a majority of eumycetoma cases. The recent cases of Sudanese patients in this series²⁰ were of *Madurella mycetomatis*, which is the most common pathogen in this region.³³

One patient in this historic series, an Iraqi-born man who suffered from a *Nocardia caviae* infection, was hypothesized by the reporters¹³ to be the first autochthonous case reported in Israel. This seems probable considering the exceptionally long time between the last possible exposure (more than 25 years), the lack of reports of mycetoma from Iraq, and the fact that the patient reported a minor local trauma that led to the development of the symptoms. Three later cases^{15–17} were presumed by the same authors to be autochthonous, a 39-year-old woman of Yemenite origin with a *Nocardia caviae* infection, and two Israeli-born patients for whom no further demographic or exposure data were given. In our view, the Yemenite origin of the first patient poses a challenge in making a definite assumption that she acquired her disease in Israel. As such, both options are listed in Table 1. The other two patients, of whom at least one is Israeli born, probably did contract their disease in Israel, along with the two unpublished autochthonous cases we reported here. Autochthonous cases of mycetoma in nonendemic areas are rare, although they have been previously reported.^{5–7} Many of these reports are from Mediterranean regions of Europe which are climatically and geographically similar to Israel. The five autochthonous cases reported in this series add to the tens of cases reported from other Mediterranean countries.⁵ It is important to note that the autochthonous cases included both actinomycetomas and eumycetomas.

Travel-related mycetoma was reported in one of the patients in our series,¹⁹ as mentioned earlier. This man was presumed to contract the infection in one of frequent

travels to southeast Asian countries including India, Burma, and Indonesia and after a local minor trauma. The identified pathogen was *Cylindrocarpum lichenicola*, a known, albeit rare, causative agent of eumycetoma. The reports of imported mycetoma cases in western countries are almost solely of immigrants from endemic countries, we have found scarce reports of mycetoma in travelers returning from endemic areas,^{34,35} all of unusual pathogens.

The marked male predominance in this series (76%) is similar to that described in the literature,³⁰ as is the mean age (42 years) which is in accordance with global reports that 70% of cases are of patients between 20 and 40 years of age.³⁰

A few relevant clinical points rise from this historic series. The first is the long incubation period seen in many of these cases. Though in most patients symptoms started in the endemic area, we have information regarding five patients who developed symptoms after leaving an endemic area. This enables us to estimate the incubation period, assuming that the last exposure was upon leaving the endemic area and that these cases are not autochthonous. In these patients, the estimated incubation period ranged between 1 and 10 years (mean 5.6 years). The incubation time of this disease can mainly be estimated in a migration setting where the infected individual is traveling to a nonendemic area. Reports of such long incubation periods are not rare in the literature.^{36–38}

Another interesting point that is apparent throughout this case series is the delay between symptom onset and the establishment of the diagnosis despite numerous interactions with medical personnel. This point is in accordance with most of the previously reported cases.³³ In other words, the diagnostic delay in mycetoma is probably the rule rather than the exception. The reasons for this delay may be more obvious in developing areas where access to medical care is poor and proper diagnostic tools are many times lacking. However, this delay characterizes our report and reports from other developed countries as well.^{38,39} We presume that the main reason for this delay lies in the rarity of this condition in developed countries and the fact that very few physicians are acquainted with the disease.

Our series demonstrates the observation that treating actinomycetomas is usually far more successful than treating eumycetomas.³ Treatment of actinomycetomas is more effective; the gold standard today is considered to be trimethoprim–sulfamethoxazole sometimes in combination with dapsone or amikacin.⁴

The challenge in treating eumycetomas even in developed countries is also evident in this small series. Of the seven patients who suffered from eumycetoma, five required amputation or debridement surgery as a definitive treatment. The first case of mycetoma in Israel, described in 1942 of a 32-year-old male field laborer who was diagnosed with *Madurella* species. After receiving the treatment of choice of those days, topical injections of potassium iodide, brilliant green (an antiseptic agent used against gram-positive bacteria), and sulfadiazine, he responded partially and was lost to follow up until returning 3.5 years later with worse findings. After another failed trial of medical therapy, the patient received a course of radiotherapy (which was considered an advanced salvage treatment then) before resorting to amputation of the infected foot. To this day, long-term treatment

with antifungal therapy combined with surgical treatment is the mainstay of treating eumycetomas but failure and recurrence rates are high, especially with more advanced disease. This dictates the urgent need for development of novel medical therapy for eumycetomas. Indeed, this is considered one of the main knowledge gaps for this disease.⁴⁰

The main limitation of this study is its retrospective nature. Some of the data regarding symptom onset, duration, and years since last exposure were partial and careful approximations were made. As the purpose of this study is mostly descriptive and since the small population size made it impossible to show statistically significant findings, we believe that this limitation has little effect on the relevance of the main points that we discussed.

In conclusion, we reported four new cases of mycetoma diagnosed in Israel and reviewed all prior 17 mycetoma cases published in Israel throughout the years. This series revealed interesting historical, epidemiological, and clinical aspects of this important and neglected tropical disease. It shows that most of the imported cases are by immigrants (or travelers) from endemic countries, though autochthonous cases exist in Israel, similar to other Mediterranean areas. This highlights the challenge of diagnosis and treating this disease in developed countries. Physicians in developed countries should be mindful of the fact that this disease may be encountered in immigrants from endemic areas and returning travelers, but also in countries which are nonendemic. In this context, the importance of patient education about avoiding walking barefoot in highly endemic areas and early wound disinfection must be part of patient education in travel clinics in the developed world.

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REFERENCES

1. Venkatswami S, Sankarasubramanian A, Subramanyam S, 2012. The madura foot: looking deep. *Int J Low Extrem Wounds* 11: 31–42.
2. Lichon V, Khachemoune A, 2006. Mycetoma, a review. *Am J Clin Dermatol* 7: 315–321.
3. Zijlstra EE, Van de Sande WWJ, Welsh O, Mahgoub ES, Goodfellow M, Fahal AH, 2016. Mycetoma: a unique neglected tropical disease. *Lancet Infect Dis* 16: 100–112.
4. Nenoff P, Van de Sande WWJ, Fahal AH, Reinell D, Schöfer H, 2015. Eumycetoma and actinomycetoma: an update on causative agents, epidemiology, pathogenesis, diagnostics and therapy. *J Eur Acad Dermatol Venereol* 29: 1873–1883.
5. Buonfrate D, Gobbi F, Angheben A, Marocco S, Farina C, Van Den Ende J, Bisoffi Z, 2014. Autochthonous cases of mycetoma in Europe: report of two cases and review of literature. *PLoS One* 9: e100590.
6. Roupheal NG, Talati NJ, Franco-Paredes C, 2007. A painful thorn in the foot: a case of eumycetoma. *Am J Med Sci* 334: 142–144.
7. Foltz KD, Fallat LM, 2004. Madura foot: atypical finding and case presentation. *J Foot Ankle Surg* 43: 327–331.
8. Dostrovsky A, Sagher F, 1942. Madura disease in Israel [in Hebrew]. *Harefuah* 13: 103–105.
9. Dostrovsky A, Sagher F, 1948. Failure of sulphonamides and penicillin in maduromycosis. *Lancet* 1: 177–178.
10. Dostrovsky A, Raubitschek KF, Sagher F, 1952. A case of black grain mycetoma caused by a *Madurella* species. *Dermatologica* 104: 415–423.
11. Ziprkowsky L, Altmann G, Daliith F, Spitz U, 1957. *Mycetoma pedis*; four cases treated with streptomycin. *AMA Arch Derm* 75: 855–863.
12. Schewach Millet M, Ziprkowski L, Feinstein A, Cvibah T, 1973. *Mycetoma pedis*, a report of two cases. *Isr J Med Sci* 9: 900–903.
13. Alteras I, Feuerman EJ, Dayan I, 1980. Mycetoma due to *Nocardia caviae*. The first Israeli patient. *Int J Dermatol* 19: 260–262.
14. Landau Z, Feld S, Frumkin A, Resnitzky P, 1986. *Nocardia brasiliensis* skin infections. *Isr J Med Sci* 22: 397–399.
15. Alteras I, Feuerman EJ, 1986. The second case of mycetoma due to *Nocardia caviae* in Israel. *Mycopathologia* 93: 185–187.
16. Alteras I, Abraham D, Ideses C, Segal R, Sandbank M, 1988. Mycetoma of the forearm due to *Actinomadura madurae*. *Mycopathologia* 103: 55–57.
17. Alteras I, Hagler J, Trattner A, Morojinski G, Segal R, Sandbank M, 1992. Mycetoma with black granules: first case in a native of Israel [in German]. *Hautarzt* 43: 446–447.
18. Tamir G, Adler A, Hagler J, Hauben DJ, Goldberg I, 1995. Mycetoma of the foot: surgical treatment with free flap reconstruction. *Eur J Plast Surg* 18: 124–126.
19. Chazan B, Colodner R, Polacheck I, Shoufani A, Rozenman D, Raz R, 2004. Mycetoma of the foot caused by *Cylindrocarpum lichenicola* in an immunocompetent traveler. *J Travel Med* 11: 331–332.
20. Brufman T, Ben-Ami R, Mizrahi M, Bash E, Paran Y, 2015. Mycetoma of the foot caused by *Madurella mycetomatis* in immigrants from Sudan. *Isr Med Assoc J* 17: 418–420.
21. Raubitschek F, 1958. A critical survey of medical mycology in Israel 1946–1956. *Mycopathol Mycol Appl* 9: 176–182.
22. Kuttin ES, Beemer AM, 1977. Systemic mycoses in Israel. *Contrib Microbiol Immunol* 4: 46–55.
23. Bryceson A, 2000. Philoetetes' foot. *Lancet* 355: 850.
24. Schwartz E, Shpiro A, 2015. Madura foot or Philoetetes foot? *Isr Med Assoc J* 17: 442–444.
25. Hershkovitz I, Speirs M, Katznelson A, Arensburg B, 1992. Unusual pathological condition in the lower extremities of a skeleton from ancient Israel. *Am J Phys Anthropol* 88: 23–26.
26. Spigelman M, Donoghue HD, 2001. Brief communication: unusual pathological condition in the lower extremities of a skeleton from ancient Israel. *Am J Phys Anthropol* 114: 92–93.
27. Clemow FG, 1906. Mycetoma (madura foot) in the Yemen. *BMJ* 1: 918–919.
28. Yu AM, Zhao S, Nie LY, 1993. Mycetomas in northern Yemen: identification of causative organisms and epidemiologic considerations. *Am J Trop Med Hyg* 48: 812–817.
29. Khatri ML, Al-Halali HM, Fouad Khalil M, Saif SA, Vyas MCR, 2002. Mycetoma in Yemen: clinicoepidemiologic and histopathologic study. *Int J Dermatol* 41: 586–593.
30. Van De Sande WWJ, Vinetz JM, 2013. Global burden of human mycetoma: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 7: e2550.
31. The Israeli Central Bureau of Statistics, 2015. *The Ethiopian Population in Israel* [in Hebrew]. Available at: http://www.cbs.gov.il/reader/newhodaot/hodaa_template.html?hodaa=201511302. Accessed May 12, 2016.
32. Israeli Authority of Immigration and Population, 2016. *Reports of Foreigners in Israel* [in Hebrew]. Available at: https://www.gov.il/he/Departments/publications/reports/foreign_workers_report_q1_2016. Accessed May 12, 2016.
33. Fahal A, Sheikh Mahgoub E, El Hassan AM, Abdel-Rahman ME, 2015. Mycetoma in the Sudan: an update from the Mycetoma Research Centre, University of Khartoum, Sudan. *PLoS Negl Trop Dis* 9: e0003679.

34. Pelzer K, Tietz HJ, Sterry W, Haas N, 2000. Isolation of both *Sporothrix schenckii* and *Nocardia asteroides* from a mycetoma of the forefoot. *Br J Dermatol* 143: 1311–1315.
35. Douwes KE, Schmalzbauer E, Linde H-J, Reisberger EM, Fleischer K, Lehn N, Landthaler M, Vogt T, 2003. Branched filaments no fungus, ovoid bodies no bacteria: two unusual cases of mycetoma. *J Am Acad Dermatol* 49: S170–S173.
36. Fletcher CL, Moore MK, Hay RJ, 2001. Eumycetoma due to *Madurella mycetomatis* acquired in Jamaica. *Br J Dermatol* 145: 1018–1021.
37. Turner PG, 1989. Madura foot or plantar fibromatosis. *J Bone Joint Surg Br* 71: 531.
38. Verdolini R, Amerio P, Bugatti L, Manso E, Cataldi I, Brancorsini D, Nicolini M, Filosa G, Giangioacomi M, 2000. Madura's foot: report of a case caused by *Madurella mycetomatis*. *Eur J Dermatol* 10: 627–629.
39. Ichinomiya A, Nishimura K, Takenaka M, Utani A, Nishimoto K, 2014. Mycetoma caused by *Nocardia transvalensis* with repeated local recurrences for 25 years without dissemination to viscera. *J Dermatol* 41: 556–557.
40. Van De Sande WWJ, Sheikh Maghoub E, Fahal AH, Goodfellow M, Welsh O, Zijlstra E, 2014. The mycetoma knowledge gap: identification of research priorities. *PLoS Negl Trop Dis* 8: e2667.