Madura foot in Europe: diagnosis of an autochthonous case by molecular approach and review of the literature

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INTRODUCTION

Mycetoma is a chronic granulomatous infection of the soft-tissue of the foot and it is endemic in tropical and subtropical countries. Some cases have also been reported in local people or migrants in temperate countries. The microbiological diagnosis requires prolonged bacterial cultures in aerobic and anaerobic conditions, but the use of the molecular approach could be helpful for an early and rapid diagnosis.

We describe an autochthonous case of *Actinomadura madurae* foot infection in an Italian woman. The diagnosis was achieved 36 months after symptoms onset by PCR detection and sequencing of 16S rDNA directly on biopsy. She started therapy with rifampin, trimethoprim-sulfamethoxazole, and amikacin. After 3 months the pain had disappeared and the swelling subsided.

We reviewed the literature on Madura foot due to bacterial causative agents in Europe and observed that the median time from onset to diagnosis is high, possibly due to several factors like the difficulties of the microbiological and radiological diagnosis. Our case report and the review of literature point out that the implementation of a surveillance system, the involvement of an infectious diseases specialist, with experience in tropical diseases, and the availability of a microbiology unit to perform feasible and rapid molecular diagnostic tests could result in an earlier diagnosis and an optimal antibiotic therapy of this rare but difficult-to-treat and, above all, difficult-to-diagnose infection.

SUMMARY

Madura foot is a chronic granulomatous infection of the soft-tissue of the foot and it is endemic in tropical and subtropical countries. Some cases have also been reported in local people or migrants in temperate countries. The microbiological diagnosis requires prolonged bacterial cultures in aerobic and anaerobic conditions, but the use of the molecular approach could be helpful for an early and rapid diagnosis.

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Key words: Madura foot, *Actinomadura madurae*, Sequencing 16S r-DNA, Ribosomal RNA

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CASE REPORT

We describe a case of Madura foot in a 48 year-old Italian woman, working as a florist. She did not refer travel or trauma. In March 2012, she presented a swelling of the dorsum of the right foot. In October 2013 an MRI scan showed an infiltrative mass between II-III and III-IV metatarsus, extending to flexor tendons, without bone involvement (Figure 1). The soft tissue biopsy showed an inflammatory reaction, but the orthopaedics who assessed the patient did not prescribe any therapy or further diagnostic procedures. In February 2014, a second biopsy confirmed an inflammatory necrotic exudative reaction and the culture was positive for methicillin-resistant Staphylococcus epidermidis. At that time S. epidermidis was considered the potential causative agent of the infection and daptomycin 8 mg/kg/day was given for 45 days in combination with rifampin 600 mg/day for 10 days, with partial improvement. After a few weeks the patient again presented pain and worsening of the swelling in the dorsum of the right foot. In July 2015, the patient was referred to the Infectious

Figure 1 - MR image of the Madura foot. A soft tissue ill-defined mass involved the dorsal aspect of the forefoot and the subcutaneous tissue, infiltrating intermetatarsal spaces and the underlying plantar muscles. No microabscesses or bone involvement were observed.

a) sagittal T1-weighted image: conglomerate areas of multiple, discrete, small round nodules (3-5 mm) isointense compared with muscle; b) coronal STIR (short tau inversion recovery) image: hyperintense conglomerate areas of nodules which were separated by a low signal intensity rim. In the centre of some of these nodules there is a tiny hypointense focus, resulting in the characteristic dot-in-circle sign, which indicates mycetoma grains; c) sagittal T1-weighted image after intravenous gadolinium contrast administration: the granulomatous tissue shows diffuse hyperintensity of signal with non-enhanced central foci corresponding to mycetoma grains.

Figure 2 - Madura foot due to Actinomadura madurae.

a) at the start of the therapy a fistula presented on the dorsum of the right foot with grains in the purulent drainage; b) After 3 months of therapy; c) After 6 months of therapy.
and Tropical Diseases Unit of Careggi Hospital, where she underwent a new biopsy for the suspected diagnosis of Madura foot. All aerobic and anaerobic cultures, incubated for 10 days, performed on Columbia agar 5%, Chocol

Table 1 - European cases of Actinomycetoma.

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Specialist making diagnosis</th>
<th>Country of birth of the patient</th>
<th>Risk factors</th>
<th>Time from onset to diagnosis</th>
<th>Bone involvement</th>
<th>Culture (media)</th>
<th>PCR</th>
<th>Etiology</th>
<th>Surgery</th>
<th>Therapy (duration, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balabanoff, 1980, Bulgaria</td>
<td>Dermatologist</td>
<td>Bulgaria</td>
<td>No</td>
<td>11 years</td>
<td>Yes</td>
<td>Positive (NR)</td>
<td>No</td>
<td>A. madurae</td>
<td>Refused</td>
<td>Nitrosole (NR)</td>
</tr>
<tr>
<td>Balabanoff, 1980, Bulgaria</td>
<td>Dermatologist</td>
<td>Bulgaria</td>
<td>NR</td>
<td>4 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>No</td>
<td>N. asteroides</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Balabanoff, 1980, Bulgaria</td>
<td>Dermatologist</td>
<td>Bulgaria</td>
<td>NR</td>
<td>4 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>No</td>
<td>Nocardia spp</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Balabanoff, 1980, Bulgaria</td>
<td>Dermatologist</td>
<td>Bulgaria</td>
<td>NR</td>
<td>7 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>No</td>
<td>Nocardia spp</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Balabanoff, 1980, Bulgaria</td>
<td>Dermatologist</td>
<td>Bulgaria</td>
<td>NR</td>
<td>2 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>No</td>
<td>A. madurae</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Binazzi, 1982, Italy</td>
<td>Dermatologist</td>
<td>Italy</td>
<td>No</td>
<td>5 years</td>
<td>Yes</td>
<td>Positive (NR)</td>
<td>No</td>
<td>A. madurae</td>
<td>No</td>
<td>Penicillin, cam, dox, SXT, rifampin, lincomycin (NR); ketoconazole (NR)</td>
</tr>
<tr>
<td>Pelzer, 2000, Germany</td>
<td>Dermatologist</td>
<td>Greece</td>
<td>Trauma</td>
<td>1 year</td>
<td>No</td>
<td>Positive (SGA, rice agar, Kimmig’s agar)</td>
<td>No</td>
<td>N. asteroides, Sporothrix schenckii</td>
<td>No</td>
<td>SXT + itraconazole (7)</td>
</tr>
<tr>
<td>Rigopoulos, 2000, Greece</td>
<td>Dermatologist</td>
<td>Albania</td>
<td>Trauma</td>
<td>4 years</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>A. madurae</td>
<td>No</td>
<td>Penicillin + SXT (25 days) A+SXT (1) Daps+mino (lost follow up)</td>
</tr>
<tr>
<td>Papaioannide, 2001, Greece</td>
<td>Internal Medicine specialist</td>
<td>Albania</td>
<td>Farmworker</td>
<td>4 years</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Actinomadura spp</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Ispoglou, 2003, Greece</td>
<td>Internal Medicine specialist</td>
<td>Greece</td>
<td>No</td>
<td>5 years</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>A. madurae</td>
<td>No</td>
<td>Daps= S (18)</td>
</tr>
<tr>
<td>Usai, 2005, Italy</td>
<td>Dermatologist</td>
<td>Italy</td>
<td>Farmworker</td>
<td>NR</td>
<td>No</td>
<td>Positive (BA, CA)</td>
<td>NR</td>
<td>A. madurae</td>
<td>No</td>
<td>I + Dox (NR); Relapse: LNZ (NR)</td>
</tr>
<tr>
<td>De Palma, 2006, Italy</td>
<td>Orthopaedic surgeon</td>
<td>Albania</td>
<td>No</td>
<td>5 years</td>
<td>Yes</td>
<td>Positive (SGA, CBA)</td>
<td>No</td>
<td>A. madurae</td>
<td>No</td>
<td>SXT + A (2) then SXT (6)</td>
</tr>
<tr>
<td>Gunduz, 2006, Turkey</td>
<td>Dermatologist</td>
<td>Turkey</td>
<td>Nail trauma</td>
<td>15 years</td>
<td>No</td>
<td>Positive (NR)</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Ciprofloxacin + itraconazole + SXT (14)</td>
</tr>
<tr>
<td>Buonfrate, 2014, Italy</td>
<td>Infectious diseases specialist</td>
<td>Albania</td>
<td>Forest ranger</td>
<td>12 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>NR</td>
<td>A. madurae</td>
<td>No</td>
<td>NR (24)</td>
</tr>
<tr>
<td>Buonfrate, 2014, Italy</td>
<td>Infectious diseases specialist</td>
<td>Albania</td>
<td>Woodcutter</td>
<td>19 years</td>
<td>NR</td>
<td>Positive (NR)</td>
<td>NR</td>
<td>A. madurae</td>
<td>Yes</td>
<td>NR (24)</td>
</tr>
<tr>
<td>Case presented in this article</td>
<td>Infectious diseases specialist (referred by orthopaedic)</td>
<td>Italy</td>
<td>Florist?</td>
<td>3 years</td>
<td>No</td>
<td>Negative (CBA, SGA, CA)</td>
<td>16S</td>
<td>A. madurae</td>
<td>No</td>
<td>Rifampin + A + SXT</td>
</tr>
</tbody>
</table>

A: amikacin; BA: blood agar; CA: chocolate agar; Cam: chloramphenicol; CBA: Columbia blood agar; Daps: dapsone; Dox: doxycycline; I: imipenem; LNZ: linezolid; Mino: minocycline; NR: not reported; PCR: polymerase chain reaction; S: streptomycin; SGA: Sabouraud glucose agar; SXT: co-trimoxazole.
Multaneously, total DNA was extracted from the biopsy with a Nuclisens® EasyMag® instrument (bioMérieux) and amplified with universal 16S rDNA primers D88 and E94 (Paster, 2001). The PCR tested positive, and the am- plionic sequence, determined on both strands, yielded a 99.1% identity with A. madurae DSM 43067 (accession no. NR_026343). After the last biopsy a fistula presented on the dorsum of the right foot with grains in the purulent drainage. The patient started therapy with rifampin 600 mg/day, trimethoprim-sulfamethoxazole (SXT) 960 mg three times a day, and amikacin 1 g for the first 15 days. After 3 months of treatment the pain had disappeared and the swelling subsided. The patient was reassessed also after about 6 months (February 2016) and the lesion had fully healed (Figure 2).

We reviewed the literature on Madura foot using the electronic database Pubmed and inserting these search terms: Madura foot, Europe, European countries, Acti- nomycetoma. We restricted the review to bacterial caus- ative agents, excluding localizations other than foot or fungal etiology. We found 16 bacterial Madura foot re- ports. Including the present report in the analysis, 11 of them were caused by Actinomadura spp (64.7%), 5 cases (31.2%) presented bone involvement (Table 1) and in one of those a below-ankle amputation was performed. Six of the 17 patients were migrants from other European coun- tries (mostly from Albania). The reviewed cases showed an extremely high median time from onset to diagnosis of 6.7 years (range 1-19 years). The difficulty of an early diagnosis is probably due to several factors, namely the rarity of illness and the difficulties of the microbiological diagnosis.

Moreover, the radiological diagnosis of Madura foot is challenging, and very often misdiagnosed as an infe- rtive lesion. A multidisciplinary approach is needed, con- sidering also that in addition to the present case only 2 other cases were referred to infectious diseases specialist, while the other patients were assessed by dermatologists (58.8%), internal medicine specialists (11.8%) and orthopaedics (5.9%). Probably the implementation of a surveil- lance system, the involvement of an infectious diseases specialist, with experience in tropical diseases, and the availability of a microbiology unit performing feasible and rapid molecular diagnostic tests could result in an earlier diagnosis and an optimal antibiotic therapy. In our case the molecular detection of the pathogen directly on biopsy specimens by PCR and sequencing allowed us to identify the causative agent and to prescribe the appropri- ate antibiotic therapy.

As for treatment, different antimicrobial drugs were used in the reported cases due to A. madurae, with a wide range of length of therapy (8-24 months), evidencing the lack of clinical studies to determine the best therapeutic approach. The most common treatment was an association of two or more antimicrobial agents, including peni- cillin, aminoglycosides, dapson, SXT, oxazolidinones, and quinolones for several months (up to 24 months) (Bettesworth, 2009; Welsh, 2012). In vitro A. madurae is sensitive to amikacin, SXT, linezolid and quinolones (Vera-Cabrera, 2004). However, Clinical and Laboratory Standard Institute breakpoints are validated for Nocardia spp and can only tentatively be used for actinomycetes (Woods, 2011). Due to the growing number of migrants to European countries and of travelers to tropical countries, an increase in autochthonous and imported cases of Mad- ura foot in Europe is to be expected.

The present report points out the importance of the knowledge of this rare but difficult-to-treat and, above all, difficult-to-diagnose infection.

References


