Case Report

Actinomadura pelletieri mycetoma – an atypical case with spine and abdominal wall involvement

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We describe a case of mycetoma caused by *Actinomadura pelletieri* with simultaneous involvement of the spine, abdominal wall and retroperitoneal space in a man who had suffered from 'Madura foot' 10 years earlier. The characteristics of this case were analysed and contextualized among those of other cases of mycetoma caused by other micro-organisms found through a review of the international literature. The rarity of the disease in industrialized countries and its possible atypical presentations may hinder a prompt diagnosis. Culture techniques that allow detection of slow-growing fungi and actinomycetes should be routinely used when dealing with tissue samples from patients from tropical and subtropical regions with chronic granulomatous infections.

Received 6 November 2010

Accepted 18 January 2011

Introduction

Mycetoma, a disease that causes disfiguration, is a serious problem in many tropical and subtropical regions (Fahal, 2004). We describe a unique case of mycetoma caused by *Actinomadura pelletieri*, with simultaneous involvement of the spine, abdominal wall and retroperitoneal space. The condition developed 10 years after successful clinical treatment of 'Madura foot'.

Case report

In May 2009, a 59-year-old Senegalese man was admitted to the Division of Internal Medicine, Policlinico 'G. Martino', Messina, Italy, because he had paraparesis, dyspnoea and fever. The patient had been transferred from Dakar University Hospital, Dakar, Senegal, where he had been hospitalized in March and later discharged with a diagnosis of prostate cancer with vertebral metastases. The patient was unable to report his remote medical history

because he was not proficient in English, French or Italian, and no relevant documentation was available.

For 5 months prior to admission to our hospital (Policlinico 'G. Martino'), he had been experiencing lower back pain that was aggravated during coughing and defecation. This symptom was followed by progressive functional impotency and pain in the lower limbs, which eventually led to paraparesis with sphincter dysfunction and relapsing fever with temperature peaks of 39.5 °C.

On admission, physical examination revealed he had a temperature of 39.0 °C, a pulse rate of 140 beats min⁻¹, a respiratory rate of 36 breaths min⁻¹, and a blood pressure of 110/85 mmHg. Numerous painless, hard-elastic, cutaneous and subcutaneous nodules of various sizes were detected bilaterally in the inguinal region in the lower abdominal area, and in the lumbar region (Fig. 1). His lower limbs, especially the right one, were swollen. His toes were dystrophic and showed signs of dyskeratosis. His liver and spleen were palpable 2 cm below the costal margin; laboratory tests revealed a total leukocyte count of 12 700 cells µl⁻¹ with 70 % neutrophils and 24 % lymphocytes, and a platelet count of 510 000 platelets µl⁻¹. His D-dimer level was 1395 µg l⁻¹ [reference range (RR) 50–259 µg l⁻¹]. His erythrocyte sedimentation rate was 120 mm h⁻¹ (RR <15 mm h⁻¹), his C-reactive protein level was 15.27 mg

Abbreviations: CT, computed tomography; RR, reference range.

The GenBank/EMBL/DDBJ accession number for the 16S rRNA gene sequence of *Actinomadura pelletieri* reported in this paper is GU265734.

Images of the isolate and of scans of the patient are available as supplementary data with the online version of this paper.

Fig. 1. Macroscopic aspect of the skin surface with swelling (white arrow), lesions (*) and fistulae (black arrows).

l^{-1} (RR 0–5 $mg\ l^{-1}$) and his fibrinogen level was 678 $mg\ dl^{-1}$ (RR 160–450 $mg\ dl^{-1}$). Multiple cultures of blood, urine, sputum and needle-aspirates of the subcutaneous nodules tested negative for bacteria, mycobacteria and fungi. Serological studies for human immunodeficiency virus (HIV-1, HIV-2), *Brucella* spp. and *Treponema pallidum* yielded negative results, as did the Mantoux test; tumour markers were not detected in the serum.

Ultrasonography of the abdominal wall revealed that the soft tissues (both superficial and deep) contained many cystic lesions, most communicating with each other through sinus tracts. Closely aggregated, fine, hyper-reflective echoes were noted at the bottom of the cystic cavities (Supplementary Fig. S1 available with the online journal). It was noted that the pressure from the probe caused exudate discharge from the superficial lesions, and bilateral hydronephrosis, probably due to extrinsic compression of the ureters.

Exudate was aspirated twice from the cystic lesions: the first sample appeared creamy white, the second appeared haemorrhagic. Microscopic examination showed the presence of a mixture of neutrophils and lymphocytes. Gram staining yielded negative results, and the results of a cytological examination were negative for malignancy.

An echo-Doppler scan of the lower limbs showed bilateral deep venous thrombosis, probably due to extrinsic compression, extending to the iliac vessels. Computed tomography (CT) confirmed the ultrasonography findings, distinctly showing extensive muscular involvement (especially of the paravertebral and psoas muscles) and spinal canal obliteration (Supplementary Fig. S2 available with the online journal). The sinus tracts were better characterized, and bilateral deep venous thrombosis was confirmed (Fig. 2). Furthermore, pulmonary CT angiography confirmed the suspicion of pulmonary embolism (not shown). Magnetic resonance imaging of the abdomen and spinal cord revealed significant vertebral involvement, with complete pathological

Fig. 2. Contrast-enhanced late-phase CT image showing subcutaneous and deep abscesses indicated by black arrows; the white arrow shows a typical sinus tract fistulized to the pelvic skin surface. The image shows bilateral thrombosis of the iliac veins, more evident in the left iliac vein, with peripheral enhancement (indicated by a small black arrow).

substitution of the 11th dorsal vertebra (Supplementary Fig. S3 available with the online journal), an epidural abscess and multiple inhomogeneous abscesses (extrafascial and intrafascial) throughout the abdominal wall (Supplementary Fig. S4 available with the online journal). Radiography of the right leg revealed osteoperiosteal involvement with bone loss at the tibial metaphysis and a lytic lesion at the proximal

Fig. 3. Primary culture of *A. pelletieri* grown on PDA. The inset shows the morphological characteristics of the colonies grown on PDA medium.

fibula; in addition, a periosteal reaction deforming the bone profile was noted (Supplementary Fig. S5 available with the online journal). No significant findings were obtained in CT of the skull.

The complexity of the clinical presentation (chronicity, the presence of multiple abscesses, and involvement of the skin, bone and soft tissues) suggested the possibility of mycetoma. This prompted us to perform specific tests for slow-growing fungi and actinomycetes. Simultaneously, treatment with itraconazole (200 mg per day) and co-trimoxazole (960 mg per day), and adjuvant therapy with analgesics were initiated.

Repeat microscopic examination of the exudate showed the presence of red purplish grains measuring 40–400 µm in diameter, consistent with the dimensions of the fine hyper-reflective echoes seen during ultrasonic examination. These grains looked like broken dishes when stained with Giemsa stain (Supplementary Fig. S6 available with the online journal).

Exudate aspirated from the lesions was seeded on potato dextrose agar (PDA) medium. Six weeks later, several pinkish colonies had grown on the medium (Fig. 3). They appeared as red dots after subculture on Löwenstein–Jensen medium (Supplementary Fig. S7 available with the online journal). Microscopic examination of the colonies after Gram staining showed extensively branched Gram-positive filaments (Supplementary Fig. S8 available with the online journal). Further examination with stereomicroscopy revealed waxy, furrowed and irregularly folded or convoluted colonies (Fig. 3). Biochemical tests indicated that the cells decomposed casein, and failed to hydrolyse urea and aesculin. The causative agent was therefore suspected to be *A. pelletieri*. *In vitro* amplification of the 16S rRNA gene, performed using universal eubacterial primers f27 and r1492 (Lane, 1991), subsequent sequence analysis with the BLAST algorithm and comparison against the GenBank database confirmed this suspicion. The nucleotide sequence was submitted to GenBank under the following GenBank/EMBL/DDBJ accession number: GU265734.

In line with this diagnosis, itraconazole treatment was discontinued, while co-trimoxazole and amikacin (15 mg kg⁻¹ per day) were administered for 21 days. The patient's condition improved over the next few weeks with the disappearance of cutaneous fistulization and the recovery of neurological function. At the 6 month follow-up, the patient's general condition was good. Continued co-trimoxazole treatment for a minimum of 12 months more was advised. At the 9 month follow-up, the patient showed us his medical records dating back 10 years, wherein a diagnosis of Madura foot of the right leg had been reported. At this time and at the 18 month follow-up, despite the patient's good clinical condition and withdrawal from analgesic treatment, CT revealed only partial recovery from the infection. Therefore, indefinite continuation of the treatment was recommended.

Discussion

Mycetoma involves a slow-progressing granulomatous infection of the skin and subcutaneous tissue. It may be caused by fungi (termed eumycotic mycetoma or eumycetoma) or higher filamentous bacteria (*Nocardia* spp., *Streptomyces* spp. or *Actinomadura* spp. and termed actinomycotic mycetoma or actinomycetoma). The true incidence of mycetoma worldwide is unclear, and the causative agents vary with regions and climate. *A. pelletieri* is the most common cause of such infection in Senegal (Dieng *et al.*, 2003).

Mycetoma differs from other cutaneous or subcutaneous diseases because of its triad symptoms of localized swelling, underlying sinus tracts and the presence of cystic grains or granules (formed by aggregation of the causative organism) within the sinus tracts (Hospenhal, 2009). The grains vary in size (30 µm–2 cm) and colour (white, yellow, red, black or brown) depending on the causative agent. In the present case, diagnosis was delayed because of the atypical localization of the infection, the microscopic size of the grains and the late recognition of cutaneous fistulization.

Although mycetoma primarily affects the lower extremities, it also occurs in the thorax, hands, forearm, gluteus, knee and head (Welsh *et al.*, 2007). Madura foot results from minor penetrating wounds caused by thorns or splinters. It is common among fieldworkers with inadequate foot protection and among individuals who carry baskets of vegetables or wood on their shoulders or head (Palmer & Reeder, 2001).

The aggressiveness and spread of mycetoma caused by *A. pelletieri* is not as marked as those of mycetoma caused by *Nocardia* spp., which tend to disseminate haematogenously from the primary site of infection to the brain, kidneys, joints, bones and eyes (Al-Tawfiq & Al-Khatti, 2010; Palmer & Reeder, 2001). However, *A. pelletieri* causes infection frequently extending up the tibia and fibula, and is thus more aggressive (spreading through bones and lymphatic vessels) than either *Actinomadura madurae* or *Streptomyces somaliensis*, which tend to cause infection up to the ankle level (Camain, 1968; Palmer & Reeder, 2001).

In the present case, *A. pelletieri* spread from the foot through the lymphatics, had an asymptomatic presence in the tibia and fibula, and then spread through the inguinal lymph nodes to the retroperitoneal and paravertebral lymph nodes, thus affecting the 11th dorsal vertebra. Mycetoma of the abdominal wall is rare (Fahal *et al.*, 1994; Strobel *et al.*, 1981); however, two similar cases have been reported – one due to *S. somaliensis*, with involvement of the retroperitoneal space and venous and urinary obstruction (Fahal *et al.*, 1994), and the other with involvement of the spine and extension into the epidural space (Sharif *et al.*, 1991). Cases of spine involvement are almost exclusively associated with *Nocardia* spp. There have been only two reported cases of *A. pelletieri*-induced mycetoma with spine involvement. The condition affected the cervical spine and developed secondary to a traumatic injury of the

scalp and penetrating wounds caused by thorns or splinters (Beketi *et al.*, 2005). Randomized clinical trials for mycetoma are lacking and case reports have rarely presented a complete description of microbiological, molecular and clinical data. The optimal management of mycetoma, with regard to drugs, the duration of treatment, the usefulness and timing of surgery, and outcomes, are debated. Amputation or surgical excision of the affected region may be required (Fahal, 2004).

Amikacin together with co-trimoxazole was first used for treating severe actinomycetoma by Welsh *et al.* (1987). They emphasized the use of one to up to four cycles of 21 days each of amikacin and the continuous use of co-trimoxazole with the cure of the patients. When periodic amikacin (or other aminoglycosides) are used, creatine clearance and audiometric studies should be performed every 3 weeks (Welsh *et al.*, 2007).

Conclusion

The rarity of the disease mycetoma in industrialized countries and the possible atypical presentation may delay diagnosis. Clinical microbiologists should be aware of the possibility of encountering a case of mycetoma, and culture techniques that allow detection of slow-growing fungi and actinomycetes should be used when dealing with tissue samples from patients from tropical and subtropical regions with chronic granulomatous infection.

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