Successful treatment of Madura foot caused by *Pseudallescheria boydii* with *Escherichia coli* superinfection: a case report

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The current management of eumycetoma is difficult and the outcome is usually poor. In order to preserve maximum function, the condition needs to be diagnosed early and treated aggressively. We describe a case of Madura foot caused by the fungus *Pseudallescheria boydii* with bacterial superinfection by *Escherichia coli*.

Case report

An 18-year-old man from Guyana presented with a 6-month history of pain and swelling on the medial aspect of his left foot and ankle. He had sustained a superficial laceration to the area from a piece of metal while working barefoot in a field 3 years previously. At a local hospital, the wound was cleansed and dressed but not sutured. A short course of antibiotics was given, and the lesion healed completely. Two and a half years later he noticed a tender, nonerythematous swelling in the same area that drained spontaneously on 1 occasion but did heal. Over the next few months several similar smaller lesions were noted in the adjacent area.

On examination, there was evidence of a healed laceration medially, overlying the sustentaculum tali. There was a nonfluctuant, firm, nontender mass medially, measuring 1 cm in dimension, with a series of adjacent smaller lesions. The entire left foot appeared swollen and was warm to touch. Examination of the sole of the foot revealed numerous healed sinuses and several palpable painless subcutaneous masses. The range of motion of ankle, subtalar and midtarsal joints was within normal limits. A radiograph showed evidence of soft-tissue swelling medial to the left ankle and diffuse osteopenia but no periosteal elevation. There was a round lytic lucency at the base of the second metatarsal. Bone scanning showed increased activity in the second and third left metatarsal areas and gallium scanning showed evidence of increased activity in the same area and lesser activity in the left ankle joint. The radiologic investigations were interpreted as consistent with soft-tissue, tendon and possible bony involvement. Culture of a fine-needle aspirate from the mass was negative for bacterial growth at 5 days. Complete blood count at that time included a total leukocyte count of 8.8×10^9/L and a slightly elevated erythrocyte sedimentation rate of 17 mm/h.

Six weeks later the patient was admitted for further investigation and management. The appearance of the foot was unchanged and he was afebrile. His leukocyte count was 12.3×10^9/L with significant eosinophilia (absolute count 3.7×10^9/L) and the erythrocyte sedimentation rate was 41 mm/h. Filarial night smears were negative on multiple occasions as were filaria serologic findings. Hookworm ova were present in the patient's stool, but the eosinophilia persisted after a course of mebendazole. The patient had no history of allergies and was not on any medications. There was no evidence of malignant disease or collagen vascular disease.

A clinical diagnosis of Madura foot was made, and diagnostic excisional biopsy and débridement were undertaken. A medial paramalleolar incision was made, and deep to the skin a sinus tract was identified and followed down superficial to the flexor retinaculum. This structure was involved with 3 large lesions, which were firm and had the consistency of enlarged lymph nodes. These were completely excised with free margins; 1 of them extended as far back posteriorly as the Achilles' tendon sheath. Structures deep to the flexor retinaculum appeared intact and were not disturbed. The wound was closed primarily.

Postoperatively, tissue necrosis and hematoma developed in the area. The wound was re-explored medially 1 week postoperatively and the sole of the foot was also explored in the area of any drain-

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ing sinuses. The initial wound was debrided and closed with a drain in place. The majority of the plantar swelling appeared to extend over an area measuring 6 × 5 × 5 cm in the mid-portion of the plantar fascia. An incision made here transversely led to numerous draining sinuses that were followed down superficial to the plantar fascia in the region of the third metatarsal shaft, but this was not interfered with.

The diagnosis of Madura foot was confirmed with histologic evidence of stained sections from tissues taken from the left ankle and the sole of the foot. The sections showed granules containing fungal hyphae scattered throughout fibrous connective tissue. The granules were surrounded by masses of eosinophils and fewer polymorphonuclear leukocytes. Culture of tissue from these 2 areas grew *E. coli* and *P. boydii*.

Initially, the patient was treated with ampicillin (2 g intravenously every 6 hours) to control the *E. coli* infection. Hygeol 1:20 (Rhone-Poulenc Rorer Consumer Inc., Montreal) antiseptic compresses were used for wound care. He was discharged from hospital 1 week later. Ciprofloxacin, 500 mg twice daily, was prescribed until the results of culture and sensitivity studies on the fungus were obtained. The fungus was confirmed as *P boydii* and by in-vitro susceptibility testing (Dr. M.G. Rinaldi, University of Texas Health Sciences Center, San Antonio, Tex.) was found to be resistant to amphotericin B and fluconazole but sensitive to miconazole and itraconazole. The minimal inhibitory concentration to itraconazole was 0.07 μg/mL with a minimal lethal concentration 0.07 μg/mL at 24 hours and greater than 10 μg/mL at 48 hours. With this information, we started the patient 2 months postoperatively on itraconazole 200 mg/d. Because of concern about bony involvement, the ciprofloxacin was continued for 1 year and the itraconazole for 8 months. His eosinophilia gradually decreased from an absolute count of 3.7×10^9/L at the time of diagnosis to 2.08×10^9/L 4 months and 0.5×10^9/L 5 months postoperatively to normal values (0.04 to 0.4×10^9/L) subsequently. His erythrocyte sedimentation rate decreased to 6 mm/h 2 months postoperatively and 2 mm/h at 1-year follow-up. At that time he was noted to have healed lesions of both the plantar area and the medical aspect of the left foot, so all antimicrobial agents were discontinued. At follow-up 7 years postoperatively, the patient was well. There was no further drainage and no development of sinus tracts, superficial swellings, distortion, discomfort or abnormalities of the involved area.

Discussion

Mycetoma (Madura foot) is an uncommon infection usually acquired in the tropics and subtropics. Although cases have been reported from temperate regions,[1,2] most have originated in the tropics. These infections can occur at any site in the body but the majority involve the foot.[3] The infection may be caused by various saprophytic fungi (eumycetoma) or bacteria, including *Actinomyces* spp. (actinomycetoma) or *Nocardia* spp.[1] The condition was first documented in Madras, India, in 1842 and acquired its name Madura foot because of its prevalence in the Indian province of Madura.[4]

There is frequently a history of trauma or a puncture wound with inoculation of organisms from the environment,[5] and a latent period of months to years before symptoms appear. Because of this time period the initiating event is often not recalled. The primary lesion may be locally invasive to soft tissue, fascia, tendon and bone or persist as an indolent small subcutaneous painless swelling.[3,5] Either of these processes gradually enlarges and softens and may rupture through the surface forming small sinus tracts or may burrow into deeper tissues to produce swelling and distortion of the limb.[5] The burrowing follows fascial planes and results in suppuration and abscess formation. When expressed, this drainage may contain grains or granules, measuring 1 to several millimetres in size. These grains represent microcolonies of the organism.[2]

The presence or absence of a fistula is a reliable indicator of the duration of the disease.[5] Fistulae rarely occur less than 3 months from the onset of clinical symptoms. Between 3 and 6 months one third of patients present with fistulae and at 1 year from the onset of symptoms almost all patients have fistulae. When first seen our patient had fistulae on the sole of his foot 3 years after the initial trauma and had had symptoms of the disease for at least 6 months. The diagnosis of Madura foot is facilitated by a characteristic triad: tumefaction, draining sinus tracts and the presence of granules.[6] Although mycetoma may become chronic and locally invasive, metastasis of this condition is unknown.[2] With progression of the infection, blood and lymph vessels and nerves may be damaged and secondary bacterial infection can occur. Without treatment, the natural course of the disease is one of slow progression over decades with increasing tissue destruction. Because of the lack of systemic involvement and fear of amputation, patients often present late and only when the lesion interferes with their daily activities.[5]

The most common causative agent of eumycetoma varies geographically. Worldwide, *P. boydii* is second only to *Madurella* spp. as a cause of fungal mycetoma, but in the United States it is the commonest pathogen.[5] *P. boydii* invades the subcutaneous tissues and the ligaments primarily, usually sparing tendons, muscle and bone.[2]

Botromycosis is a similar chronic suppurative granulomatous disease of the skin and soft tissue usually caused by bacteria, including *E. coli*. Unlike mycetoma, the microcolonies seen are not true granules. We believe that our patient had a bacterial superinfection of his mycetoma rather than another, separate process.

Eumycotic mycetoma is difficult to manage and usually requires a combination of prolonged medical and surgical treatment.[3,5] The results are often poor, probably because until recently no effective orally active antifungal agents were available. If surgical resection is incomplete, recurrence rates are high. Before ini-

tiating chemotherapy, the infecting organism must be isolated so that the appropriate anti-infective agent can be chosen. The disease is chronic, so there is ample time to await the culture results. Many cases do not respond to commonly used antifungal compounds and in-vitro resistance has been extensively documented. Until recently the only effective agent available against *P. boydii* was intravenously administered miconazole.[7] However, this agent is toxic, being associated with major side effects of pruritus and hematologic and hepatic toxicity. Also, intravenous administration is not practical for long-term therapy. Hay and Mackenzie[1] analysed 44 cases of mycetoma in the United Kingdom seen between 1963 and 1981. The majority of their patients were from the West Indies, and in those patients the commonest organism identified was a pale granular genus of fungus of which *P. boydii* is a member. Included in their study was a patient with lesions similar to those in our patient, in whom prolonged treatment with miconazole intravenously, griseofulvin orally and surgical débridement failed. Two cases of pseudallescheriasis involving the lower extremity have been reported from Canada.[8] In one case the disease responded to combined surgical débridement and intravenously administered miconazole.[9] More recently, cases have been reported in which itraconazole has been successful.[10] This is a new triazole-type antifungal agent, which acts by interfering with C14 demethylation of lanosterol, a critical step in the synthesis of ergosterin in fungal cell membranes.[9] It can be given orally, and the recommended dose for mycetoma is 100 to 200 mg/d, often for many months.

Surgical débridement is an important adjunct to therapy.[11] Surgical therapy must be aggressive because there is an 80% relapse rate after inadequate removal of the diseased tissue.[5] Surgical therapy without chemotherapy can be curative if the surgery is radical and extensive.[6] In far-advanced disease, amputation is the only successful treatment.

The granules in mycetoma are usually surrounded by a polymorphonuclear infiltrate and may be accompanied by a granulomatous reaction with varying proportions of epithelioid cells, plasma cells and giant cells.[5] The granules in our patient were surrounded by eosinophilia and only a few polymorphs. Eosinophilia is uncommonly seen in Madura foot, but because of the histologic appearance in this case and lack of evidence for other causes it was considered important in the host response to his infection. The resolution of his peripheral eosinophilia gave us an easy parameter to follow his course.

Since the treatment of Madura foot is difficult and the clinical relapse rate is high, it is important that these infections are recognized early and treated aggressively to preserve maximum function. We attribute our success in this case to early intervention with removal of as much visibly involved tissue as possible in combination with effective antifungal therapy. Given the large number of patients from the tropics now immigrating to North America, it is essential for family physicians, infectious disease specialists and orthopedic surgeons to be aware of this disorder. Itraconazole is a new oral antifungal agent that holds promise in the treatment of this infection, but further studies are required.

References

1. Hay RJ, Mackenzie DWR. Mycetoma (Madura foot) in the United Kingdom — a survey of forty-four cases. *Clin Exp Dermatol* 1983;8(5):553-62.
2. Rippon J. *Medical mycology*. 3rd ed. Philadelphia: WB Saunders; 1988. p. 653-4.
3. Zaias N, Taplin D, Rebell G. Mycetoma. *Arch Dermatol* 1969;99:215-25.
4. Carter H. On a new and striking form of fungus disease, principally affecting the foot, and prevailing endemically in many parts of India. *Trans Med Phys Soc* 1960;6: 104-42.
5. McGinnis MR, Fader RC. Mycetoma: a contemporary concept. *Infect Dis Clin North Am* 1988;2(4):939-54.
6. Rippon JW, Carmichael JW. Petriellidiosis (allescheriosis): four unusual cases and review of literature. *Mycopathologia* 1976;58 (2):117-24.
7. Lutwick LI, Rytel MW, Yanez JP, Galgiani JN, Stevens DA. Deep infections from *Petrellidium boydii* treated with miconazole. *JAMA* 1979;241(3):272-3.
8. Bakerspiegel A, Schams D. Petriellidiosis (pseudallescheriasis) in South Western Ontario. *Sabouradia* 1984;22:247-9.
9. Drouhet E, Dupont B. Evolution of antifungal agents: past, present, and future [review]. *Rev Infect Dis* 1987;9(Suppl 1):S4-14.
10. Turner PG. Madura foot or plantar fibromatosis. *J Bone Joint Surg [Br]* 1989;71 (3):531.
11. Visvanathan R. Surgical treatment of fungal mycetoma. *Can J Surg* 1989;32(1):74-6.