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CASE REPORT

Fungal arthritis of the knee caused by *Mycoleptodiscus indicus*

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Abstract *Mycoleptodiscus indicus* is a recognized plant pathogen which has very rarely been reported as a cause of human infection. It is a tropical or subtropical fungus which is difficult to culture and identify from clinical specimens. This is the first report of septic arthritis with this fungus in a healthy Canadian male. The fungal infection was contracted on a vacation in Costa Rica, probably through direct inoculation through injured skin. The fungus was isolated from synovial fluid and identification was confirmed by DNA sequencing. There has only been one previous case of septic arthritis of the knee and one skin infection reported with this fungus; both cases involved immunocompromised hosts. Both septic arthritis patients required joint surgery and lavage to eradicate the fungus, however, only the immunocompromised patient required antifungal medications. In the future, it is very likely that the number of patients identified with *M. indicus* infection will rise due to increasing awareness of this pathogen as well as increasing exposure. Many immunocompromised patients on antiretroviral or biologic therapy are healthy enough to travel, thereby exposing themselves to exotic and infected plants which increase the risk of unusual fungal infections.

Keywords Fungal arthritis · *Mycoleptodiscus indicus* · Septic arthritis

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A 54-year-old healthy male returned to Canada after a 3-week vacation in Costa Rica. He presented with a painful, tense effusion of his left knee. He was otherwise well. He had mild patellofemoral osteoarthritis in the knees and both feet, but no systemic or immunocompromising illnesses. The synovial fluid from the knee was inflammatory, with $19{,}250 \times 10^6$/L white blood cells, predominantly neutrophils. His erythrocyte sedimentation rate (ESR) was 57 mm/h. He was rheumatoid factor negative, anti-nuclear antibody negative, and human leukocyte antigen (HLA)-B27 negative. The knee had been injected once with methylprednisolone by the family physician after the fluid was aspirated and sent for cultures. One of six cultures grew an unusual non-sporulating fungus. Three hospital-based microbiology laboratories in Vancouver were unable to identify the fungus, and it was forwarded for further evaluation to the University of Alberta Microfungus Collection and Herbarium (UAMH), Edmonton, Alberta where it was accessioned as UAMH 10746.

The eventual identification of UAMH 10746 as *Mycoleptodiscus indicus* was determined by phenotypic characteristics and DNA sequencing. The fungus was thermotolerant, growing well at 35°C but poorly at 42°C. It grew well on potato dextrose agar at 7 days, but failed to

sporulate (Fig. 1a). Subculture on sporulation media and prolonged incubation under ambient light induced development of the characteristic sporodochia, producing curved conidia with slender terminal appendages (Fig. 1b). The fungus was sensitive to the following antibiotics: amphotericin B 0.5, 5-fluorocytosine 32, itraconazole 0.5, ketoconazole 0.5, fluconazole >64, voriconazole 0.5, caspofungin 2.0 mg/L, respectively.

Two weeks after the family doctor injected the knee with methylprednisolone, the knee continued to be very painful and effused and the patient was referred to the rheumatologist. The knee was drained of fluid three times within the following 3 weeks, and the synovial fluid was sent for further cultures. These samples failed to grow organisms including bacteria, fungi, and *Mycobacterium* spp. During this period of time, the patient underwent further investigations of his knee for a possible fungal infection. Knee radiographs were unremarkable, showing no joint space narrowing, chondrocalcinosis, or erosions. A bone scan showed intense uptake of technetium (^{99m}Tc-MDP) in the medial tibial plateau (Fig. 2a), and a concurrent gallium 67 citrate scan was also abnormal, supporting a diagnosis of septic arthritis and osteomyelitis in the knee (Fig. 2b). Magnetic resonance imaging (MRI) of the knee showed markedly abnormal synovium (Fig. 3a), a large effusion (Fig. 3b), edema of the medial tibial plateau (Fig. 4a), enhancement consistent with osteomyelitis (Fig. 4b), and an erosion of the posteromedial tibial plateau (Fig. 5).

The patient was taken to the operating room where involved bone and synovial tissue was removed, and samples were sent for fungal and bacterial cultures. The knee was then thoroughly irrigated with 6 L of sterile saline. The patient was not treated with antibiotics, and they were not instilled into the joint as the final identification of the possible fungal organism and sensitivity to antimicrobials was still pending. Within 2 weeks of the arthroscopic surgery, the patient improved with significant resolution of the painful effusion and normalization of the ESR. A small, cool effusion remained and the patient was started on 15 mg oral methotrexate per week in addition to naprosyn 500 mg twice daily, 1 week after surgery. The patient's signs and symptoms of septic arthritis and osteomyelitis resolved completely within 2 months of surgery.

M. indicus is an exceedingly rare cause of human infection. The fungus is a tropical or subtropical plant pathogen, especially associated with *Zamia* species in Central and South America, India, Southeast Asia, parts of Africa, and the southern USA. The species is unknown to occur on plants in Canada, and therefore, it is unlikely to occur as a contaminant in a clinical culture. There have only been two brief case reports of human infection with this fungus; both involved immunocompromised patients [1, 2]. The first case was a male from North Carolina with systemic Wegener's granulomatosis, receiving therapy with cyclophosphamide and glucocorticoids at the time of his fungal knee infection. Exposure to fungal spores in the soil from gardening on his knees was postulated to be the mechanism of infection. Eradication of the fungus required concomitant amphotericin B with surgical debridement and joint irrigation, plus postoperative treatment with itraconazole [1].

In the second case, multiple nodular fungal skin lesions occurred in a highly immunocompromised liver transplant patient, infected with hepatitis C and human immunodeficiency virus (HIV) [2]. Resolution of his infection occurred with modulation of his immunosuppression and parenteral therapy with amphotericin B followed by several months of oral voriconazole.

In contrast to these two cases, our patient was not immunocompromised through disease or medications. He was exposed to the sharp leaves of tropical plants in Costa Rica, and his legs were scratched. The knee was most likely inoculated with fungal spores through further scratches to the legs after playing with a feral cat. Our patient recovered without antifungal medications after surgery to remove infected tissue followed by joint irrigation. No other organism was identified as a cause of his joint infection. Although *M. indicus* was isolated from only one specimen taken at the time of the patient's first presentation, the rarity of this fungus as a human pathogen and its unlikely

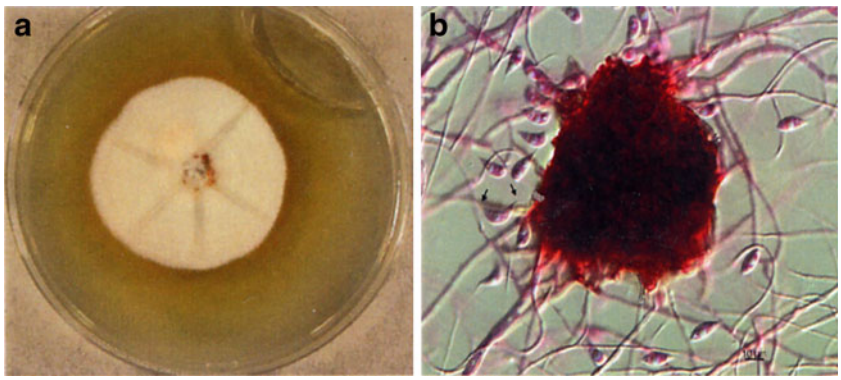

Fig. 1 **a** *M. indicus* showing colony growth on potato dextrose agar (7 days at 35°C). **b** *M. indicus* showing sporodochium producing curved conidia, with narrow appendages at both ends (differential interference contrast, lactofuchsin stain)

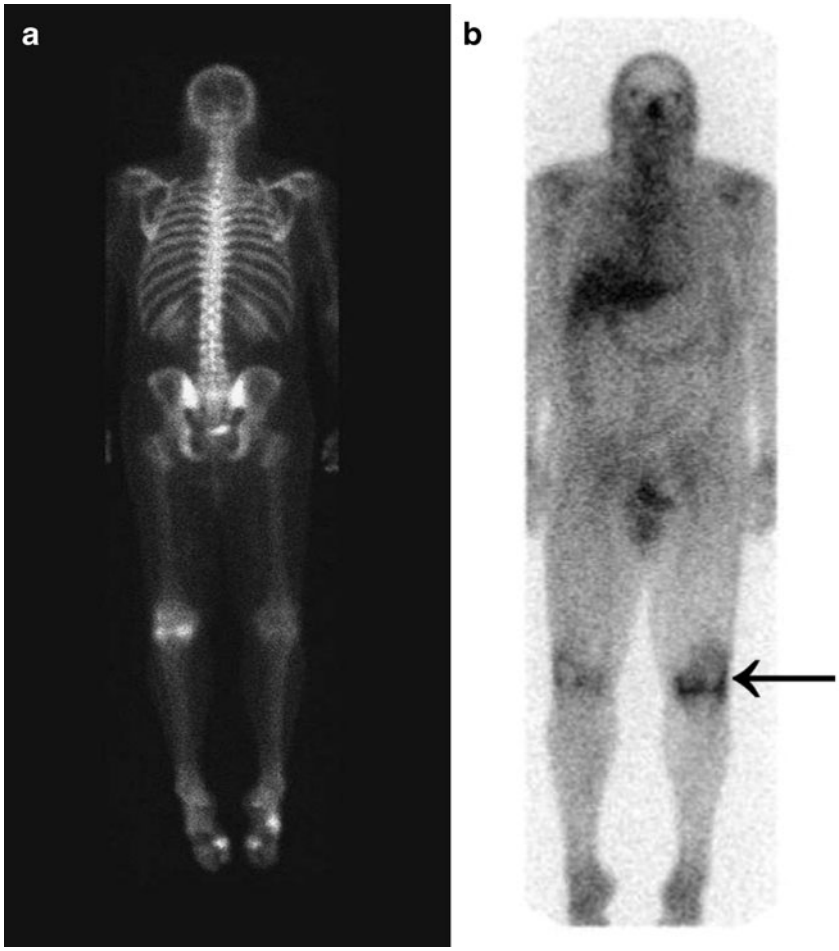

Fig. 2 **a** ^{99m}Tc-MDP bone scan (posterior view) showing marked uptake, medial tibial plateau. **b** Gallium 67 citrate scan (anterior view) done concurrently with bone scan. Intense uptake consistent with septic arthritis and osteomyelitis, left knee, medial tibial plateau

occurrence as a contaminant suggest that it was the etiologic agent. It is frequently very difficult to isolate and identify the organism responsible for septic arthritis, especially if the organism is an atypical fungus. For example, septic arthritis synovial fluid cultures with *Coccidioides immitis* are positive in <5% of cases [3].

We are aware of two (possibly three) additional cases of skin infection with this fungus. *M. indicus* was isolated in an "extended cutaneous lesion" from an immunocompromised renal transplant patient (mentioned as personal communication in De Hoog et al. [4]). During investigation of the present case, L.S. reexamined two clinical isolates which were received several years earlier and accessioned at the UAMH. Neither isolate had sporulated, but both were suspected to be *M. indicus*. DNA sequencing confirmed the identity of both isolates as *M. indicus*. One isolate came

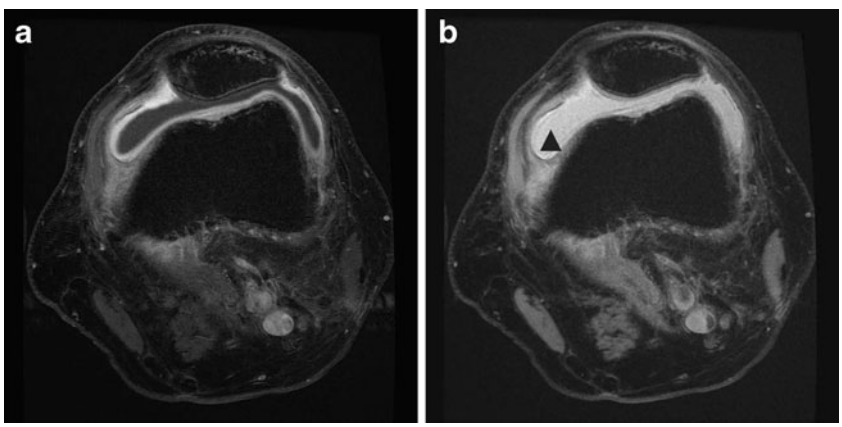

Fig. 3 **a** Patellofemoral articulation, axial T1 MRI with gadolinium showing synovial thickening and enhancement. **b** Patellofemoral articulation, axial T2 MRI with fat saturation in the same area, showing a large joint effusion (*black triangle*)

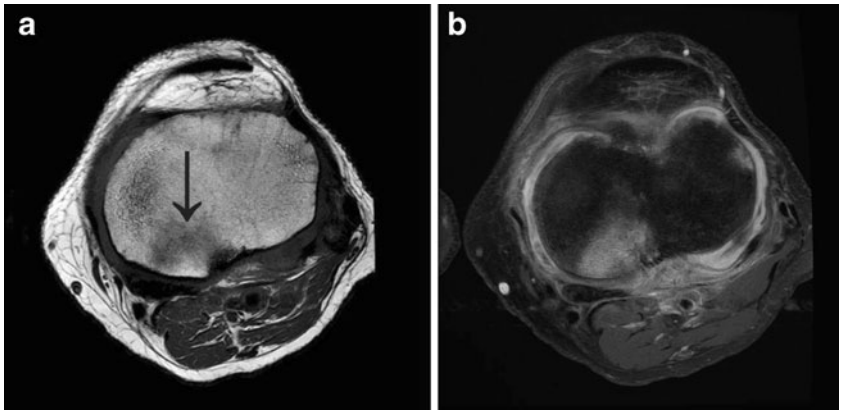

Fig. 4 **a** Proximal tibia, axial T1 MRI showing bone edema (*black arrow*). **b** Proximal tibia, axial T1 MRI post-gadolinium and fat saturation showing enhancement of the same area, consistent with osteomyelitis in the posteromedial tibial plateau

from a skin lesion on the wrist of a male patient with cancer. The second came from the foot of a patient with "fatal cancer" (lymphoma). That patient had a second skin lesion on the wrist, and both tissue samples from that patient were histopathologically positive for fungal elements. It is possible that these two cancer patients are the same individual as the foot and wrist skin samples were independently sent to L.S. with very little clinical detail from two different clinicians in the USA.

This is only the second case report of septic arthritis with this fungus, and it is the first case in the world literature involving infection of an immunocompetent individual. It is obvious from this review that *M. indicus* is a rare cause of human infection, even though it is a well-recognized plant pathogen. It would appear that skin lesions are the most likely presentation of infection with this fungus based upon the brief reports to date [1, 2, 4].

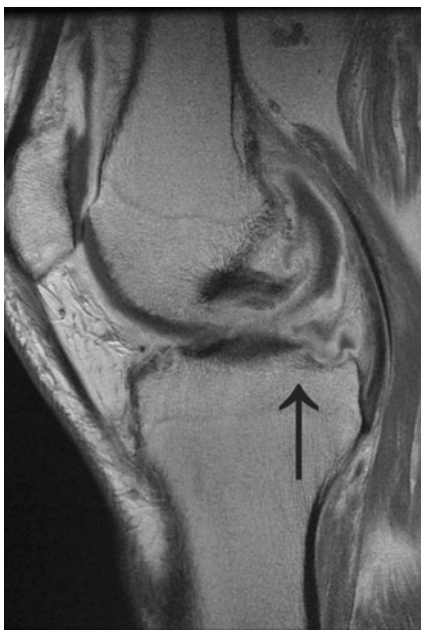

Fig. 5 Lateral aspect of medial compartment, sagittal T1 MRI post-gadolinium, showing erosion in the posteromedial tibial plateau (*arrow*) plus synovial enhancement posterior to the femoral condyle, superior to the erosion

Given the increasing popularity of travel to tropical or "third-world" destinations and the likelihood of exposure to contaminated plant material, clinicians need to be made aware of the potential for individuals to become infected with exotic fungi. This is particularly important in the era of highly immunosuppressive "biologic" therapy for rheumatological and other autoimmune diseases. In addition, extremely immunosuppressed individuals are surviving with appropriate transplant rejection and antiretroviral therapy, leaving them highly vulnerable to fungal infections. The patient reported by Garrison et al. [2] falls into the second category of susceptible patients. He was infected with HIV plus hepatitis C, and he was the recipient of a liver transplant. He recovered from his nodular skin infection with a combination of amphotericin B lipid complex plus voriconazole for 4 months.

The precise identification of *M. indicus* as the infecting organism is difficult due to the rarity of this fungus and the need for specialized culture conditions in dedicated mycology laboratories. In the present case, this led to a delay of several months in identifying the organism as *M. indicus*; fortunately, our patient was otherwise healthy and the clinical outcome was favorable. In the earlier case reports involving immunocompromised hosts, antifungal therapy was required to eradicate the infection. The only other patient reported with a *M. indicus* joint infection was immunocompromised, and he required surgical debridement and irrigation of the knee joint, plus two antifungal medications to survive [1]. Our patient has been followed closely by the same clinician (C.D.) for 36 months since his infection was first reported to the Rheumatology community [5], and he has not developed any underlying malignancy, immune-compromising illness, or chronic inflammatory arthritis. He is not diabetic or alcoholic. He has not had a relapse with fungal infection in the knee or any other site, even though he was not treated with antifungal medication. It is presumed that thorough lavage

of the joint along with removal of infected tissue during surgery, followed by anti-inflammatory medication, was an effective therapy for this otherwise healthy patient. It is apparent that the implication and identification of *M. indicus* as the cause of human infection requires the collaboration of clinicians and scientists, including mycologists and plant pathologists.

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