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CASE REPORT

Long-Term Carriage of *Medicopsis romeroi*, an Agent of Black-Grain Mycetoma, Presenting as Phaeohyphomycosis in a Renal Transplant Patient

Joshua A. Lieberman · Joseph Fiorito · Doug Ichikawa · Ferric C. Fang · Robert M. Rakita · Lori Bourassa

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Abstract *Medicopsis* species are rare fungal pathogens that frequently resist common antifungal therapies and are difficult to identify morphologically as conidia are produced in pycnidia, a key feature of coelomycetes. Immunocompromised patients are at risk of these infections, even after remote exposure, and typically present with phaeohyphomycoses without dissemination. We present the case of a renal transplant recipient 6.5 years post-transplant who developed a slowly progressive soft tissue infection mimicking a synovial cyst. A cultured isolate was identified as *Medicopsis romeroi* by sequencing of multiple ribosomal loci. The patient responded well to debridement and posaconazole therapy. Solid-organ transplant patients are at risk of opportunistic fungal infection long after transplant, and molecular methods are often required for definitive identification.

Keywords Coelomycete · Phaeohyphomycosis · Medicopsis · Solid-organ transplant · Mycetoma · Dematiaceous

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J. A. Lieberman · F. C. Fang · L. Bourassa (✉)
Division of Clinical Microbiology, Department of Laboratory Medicine, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195, USA
e-mail: bourassa@uw.edu

J. A. Lieberman
Department of Pathology, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195, USA

J. Fiorito · D. Ichikawa
Department of Podiatry, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195, USA

F. C. Fang · R. M. Rakita
Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195, USA

Introduction

Coelomycetes are environmental fungi that produce conidia in a cavity, or pycnidium. This creates a diagnostic challenge for the clinical laboratory, as routine culture conditions do not typically yield identifiable structures [1, 2]. In immunocompetent patients, a subset of these dematiaceous fungi, primarily belonging to the order *Pleosporales*, usually cause black-grain eumycetoma [3, 4]: granulomatous cutaneous infections with draining sinuses, pigmented "grains" consisting of the fungus mixed with inflammatory debris, and the potential for significant local tissue destruction [5, 6]. Although coelomycete infections are rare after solid-organ transplant (SOT) [2, 7–9], SOT recipients account for nearly half of coelomycete infections [10], along with other causes

of immunosuppression including treated rheumatoid arthritis [11] and sarcoidosis [12]. Unlike the black-grain mycetoma presentation seen in immunocompetent patients, coelomycete infections in SOT patients appear to present as phaeohyphomycoses, often with cystic spaces and without dissemination [8, 10, 12]. This contrasts with other agents of eumycetoma, which may spread hematogenously in immunocompromised patients [6].

The coelomycete genus *Medicopsis* contains environmental fungi and opportunistic human pathogens, was recently separated from *Pyrenochaeta* [13], belongs to the order *Pleosporales* [3, 4], and can cause infections in humans, typically subcutaneous infections in people living in tropical or subtropical regions [10]. Subcutaneous infections due to the opportunistic pathogen *M. romeroi* can be subclinical, with a prolonged course that may mimic other soft tissue pathology such as synovial cysts [6, 8]. We present a case of a renal transplant patient who lived in a temperate region and developed phaeohyphomycosis due to *M. romeroi* that slowly progressed over 7 months. We highlight the histopathologic findings and the role of molecular identification for this organism. The absence of local tissue destruction, hematogenous spread, sinuses tracts or grains, slow progression, and presumed long-term carriage of this organism raises important questions about the pathogenesis of this group of fungi and highlights the need for vigilance in monitoring SOT patients for indolent fungal infections.

Case Report

A 65-year-old woman with end-stage renal disease due to chronic pyelonephritis and reflux nephropathy underwent a renal transplant 6.5 years prior to her presentation. Her immunosuppressive medications consisted of tacrolimus, leflunomide, and prednisone. The patient described tripping and injuring her toe in the shower 7 months earlier and noticed some soft tissue swelling; she denied other trauma. During the intervening months, the swelling increased, along with more pain and erythema. She denied systemic symptoms, including fever, night sweats, or chills. She lived in a residential area and was an avid gardener. Although born and raised in the Philippines, the patient resides in the Pacific Northwest region of the USA and denied recent travel.

Physical examination revealed a large fluctuant and erythematous area over the right foot, between the first and second digits and wrapping around to the plantar first metatarsal (Fig. 1a). Laboratory testing demonstrated a white blood cell count of 8.73×10^3 cells/mcL (reference range $4.3–10 \times 10^3$ cells/mcL) without other significant laboratory abnormalities identified. Magnetic resonance imaging (MRI) of the foot demonstrated a $4.1 \times 3.6 \times 2.3$ cm, smoothly marginated lesion between the first and second metatarsal phalangeal joints, without significant pathology in the surrounding soft tissue or bone (Fig. 1b–d).

The lesion was aspirated and yielded 2 mL of a brown, viscous fluid. Direct staining of the fluid aspirate demonstrated neutrophils but was negative for fungal forms, bacteria, mycobacteria, or crystals. Fuzzy, white and gray mold colonies (Fig. 2a) were identified after 6 days of growth at 25 °C on inhibitory mold agar (Hardy Diagnostics, Santa Maria, CA). Lactophenol blue preparation revealed hyphae without distinguishing spores (Fig. 2b), and the colony was submitted for molecular diagnostic testing by polymerase chain reaction (PCR) amplification of the internal transcribed spacer (ITS) regions 1 and 2 and D1/D2 regions of the 28S ribosomal gene (GenBank accession numbers: MN251605 and MN251604). Subsequent Sanger sequencing and bioinformatics analysis identified the mold as *Medicopsis romeroi* (UTHSCSA DI 19-113) based on 99.35–100% nucleotide identity to published sequences deposited in the National Center for Bioinformatics (NCBI) Reference Sequence Database, available type strains, and sequences of clinical isolates deposited in an in-house sequence database; the nearest non-*Medicopsis romeroi* sequence had nucleotide identity of $< 96\%$ in each sequenced locus.

The lesion was surgically excised. Intraoperatively, the lesion was spongy and cystic, 2.5 cm in diameter, with the consistency of a ganglion cyst. Gross pathology demonstrated a 4.8-cm portion of fibrous tissue lined by a pasty yellow material with a central $4.5 \times 1.3 \times 0.5$ cm cyst opening to the external surface. Histopathology demonstrated a cystic lesion surrounded by dense, fibrous tissue with histiocytic and fibroblastic proliferation indicative of chronic inflammation and a mixed lymphocytic and neutrophilic infiltrate with scattered giant cells (Fig. 3a).

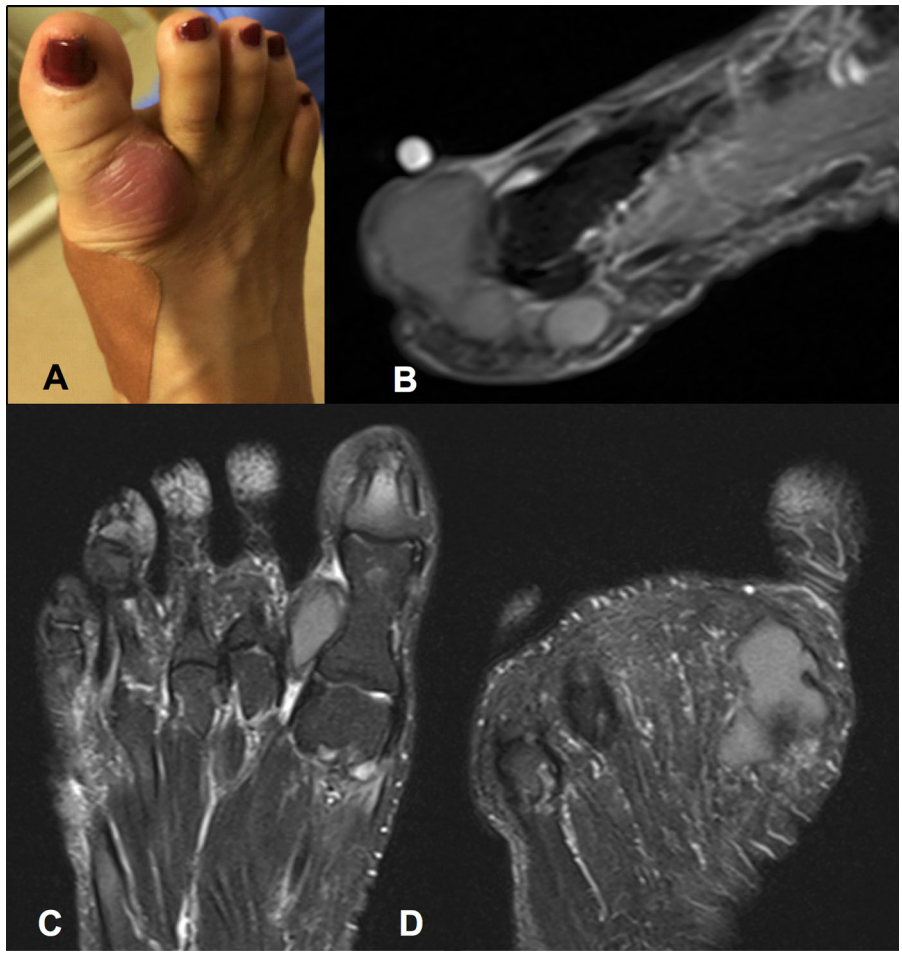

Fig. 1 Physical examination findings **a** of a swollen, erythematous, mildly painful lesion between the first and second digits at the level of the metatarsal–proximal phalangeal joints. MRI demonstrated **b–d** a 4.1-cm maximum dimension, fluid-filled cystic structure with smooth margins and without bone involvement. Images in the sagittal plane **b** show the lesion wraps around from dorsal to plantar surface; axial images demonstrate the dorsal **c** and plantar **d** extent of the soft tissue lesion

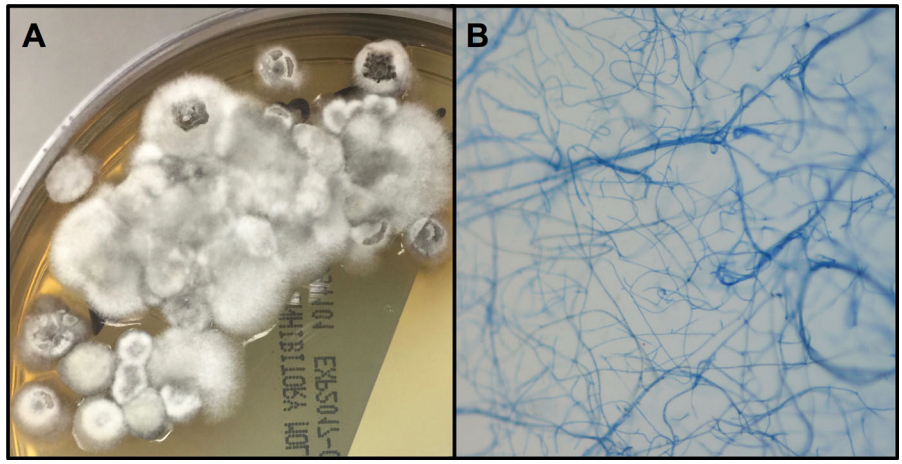

Fig. 2 Culture of the aspirate on inhibitory mold agar (IMA) grew a cottony, white mold with areas of brown pigment on the obverse (**a**). Lactophenol blue preparation (**b**) revealed hyphae only without identifying structures

Routine H&E stains contained rare and irregular hyphal forms (Fig. 3b–c). Silver staining with Gomori methenamine silver (GMS) highlighted abundant hyphal and yeast-like forms associated with the inflamed tissue (Fig. 3d–f). No melanin pigment was present.

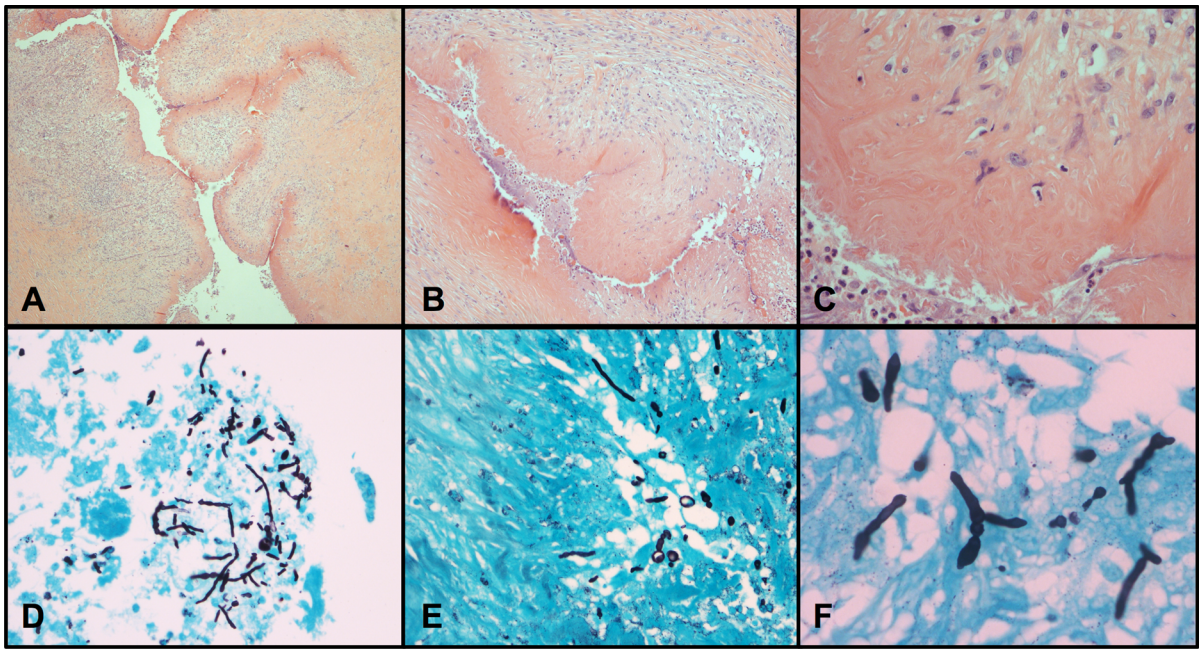

Fig. 3 Histopathologic examination revealed a cystic lesion surrounded by fibrosis with associated granulation tissue and purulent inflammation (**a**–**c**). At high power, hyphae can be faintly observed enmeshed in the tissue (**c**). Hyphae are identified on silver stain (Gomori methenamine, **d**–**f**). Rare candidate conidia are also present (**e**)

In addition to surgical debridement, the patient was initially treated with voriconazole. However, antifungal sensitivity testing performed by broth dilution (described in Clinical and Laboratory Standards Institute (CLSI) document M38-A2) demonstrated that this isolate had minimum inhibitory concentrations (MICs) of 0.5 mcg/mL (posaconazole), 2.0 mcg/mL (voriconazole), and > 16 mcg/mL (itraconazole). Based on these results, therapy was switched to posaconazole for 3 months. The patient remains free of recurrent infection > 2 years later.

Discussion

Infections with *Medicopsis romeroi* (previously *Pyrenochaeta romeroi*) are unusual in humans, but typically have an indolent course [10, 14] and, as observed in this case, cause cystic lesions in the human host [8, 12, 14, 15]. *Medicopsis* is a coelomycete fungus that produces conidia within a pycnidium (asexual fruiting body) formed by either fungal tissue, host tissue, or both [1]; within the coelomycete group, *Medicopsis* is one of the most common human pathogens [16]. In addition to cyst formation, a common feature is a prolonged, often mild clinical course lasting for months to years [4, 8]. Surprisingly, these infections may present years after a patient has departed from an endemic tropical or subtropical region [8]. The case presented above of a woman living in a temperate area emphasizes this feature.

Cases of *Medicopsis* infection have included patients with diverse baseline health ranging from no known underlying disease [10] to diabetes [14], chronic steroid therapy [6, 9], SOT [10], and leukemia or lymphoma [10]. Unlike either *Medicopsis* infections in immunocompetent patients or infections with other agents of black-grain mycetoma [5, 17], SOT patients with coelomycete infections appear to predominantly present with localized, indolent, phaeohyphomycosis that forms cystic spaces and does not disseminate [8]. Consistent with this observation, disease progression in the present case was limited and slow despite chronic immunosuppression, without invasion of surrounding tissues, and demonstrated a diffuse histiocytic inflammatory response (Fig. 3).

As in this case, most reported *Medicopsis* infections have been successfully treated with surgical excision and antifungal agents, although in a few cases surgical or antifungal monotherapy has been curative

[8, 10, 12, 14, 15]. MICs of multiple antifungal agents have been reported for several coelomycetes, including *Medicopsis*; however, clinical breakpoints for antifungal drugs in these infections have not been established for these fungi. *Medicopsis romeroi* has typically exhibited low MICs for amphotericin B, voriconazole, and terbinafine; low-to-intermediate MICs for posaconazole; and generally higher MICs for fluconazole, itraconazole, ketoconazole, and echinocandins [5, 8, 10, 12, 16]. The present isolate had a higher MIC for voriconazole than usual, thus leading to a change in therapy to posaconazole.

Morphologic identification of coelomycetes is difficult given the absence of identifying conidia [8, 10, 11] as also seen in this case (Fig. 2). Therefore, molecular diagnostic techniques targeting the ITS and 28S ribosomal DNA have emerged as key diagnostic tools [9, 11]. Several other loci have been used to refine the identification and phylogeny of coelomycete group members, including translation elongation factor 1-alpha (*TEF1*) and RNA polymerase subunit (*RPB2*) [3], although these are not currently validated for clinical use by most clinical laboratories in the USA that perform molecular fungal identification. However, as optimal treatment strategies for specific coelomycete infections become available, adopting these loci in clinical practice may improve patient care.

If present on histopathology, melanin pigment in conjunction with irregular hyphal forms in a cystic lesion provides important clues for classification, but is not specific; therefore, fungal PCR performed on formalin-fixed paraffin-embedded (FFPE) materials is an important adjunct. Fungal PCR performed on DNA extracted from FFPE tissue is especially important when cultures are not submitted, an important consideration given the capacity of these infections to mimic surgical diseases such as a ganglion cyst for which intraoperative cultures may not be performed. PCR is also important in clinical laboratories for coelomycetes like *M. romeroi* that typically do not produce uniquely identifying structures on laboratory culture media. Beyond molecular techniques, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) remains an important and rapid technique for identification of bacteria and yeast in clinical microbiology laboratories. While considerable challenges limit the application of MALDI-TOF MS to mold identification, recent reports have demonstrated promising results for identification of dematiaceous fungi and etiologic agents of black-grain mycetoma, including *Medicopsis*, by MALDI-TOF MS [17].

In summary, we present a rare case of a slowly progressive soft tissue infection caused by *Medicopsis romeroi* mimicking a ganglion cyst in a kidney transplant patient living in a temperate region. The patient was successfully treated with posaconazole and surgical excision. This organism is highly unusual outside of the tropics/subtropics, and this case likely represents long-standing carriage after travel.

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Compliance with Ethical Standards

Conflict of interest The authors declared that they have no conflicts of interest.

Ethical Approval This case report was prepared in compliance with the policies of the Institutional Review Board of the University of Washington Medical Center.

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