

Case Report

***Phialemonium curvatum* arthritis of the knee following intra-articular injection of a corticosteroid**

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Phialemonium curvatum arthritis of the knee developed in a diabetic man following intra-articular injection of a corticosteroid. Cure was achieved with a 6-week course of intravenous amphotericin B deoxycholate. *P. curvatum* is commonly found in the environment and is often considered a contaminant; yet, its pathogenic potential should be seriously considered in selected patients.

Keywords arthritis, intra-articular injection, steroids, mold, *Phialemonium curvatum*

Introduction

Although widely distributed in the environment, *Phialemonium* species rarely cause human disease. While they are seldom pathogenic in individuals with an intact immune system, they have been increasingly reported to cause disseminated infections in immunocompromised patients. Systemic *Phialemonium* infection can involve various organs, but bloodstream infections, with or without endocarditis, are most often reported in the literature [1].

Phialemonium curvatum is a dematiaceous or phaeoid (dark-walled) fungus although it lacks conspicuous dark pigmentation, as does another pathogenic member of the genus, *Phialemonium obovatum* [2]. This mold is a common inhabitant of the environment, and has been isolated from air, soil, industrial water, and sewage [3]. *Phialemonium* species are able to grow in routine blood cultures, and routine culture methods appear adequate for its isolation. [1]. The identification of *Phialemonium* species, like that of other medically important dematiaceous fungi, is based primarily upon colony and microscopic morphology. Limited *in vitro* data suggest that *Phialemonium* species

are inhibited by low concentrations of voriconazole and posaconazole, whereas the MICs of amphotericin B deoxycholate and of caspofungin are often high and those for fluconazole and itraconazole are intermediate [1]. The clinical significance of these *in vitro* data for treating *Phialemonium* infection is currently unknown. This report describes a unique case of *Phialemonium curvatum* arthritis of the knee that developed in a diabetic man following intra-articular injection of a corticosteroid.

Case report

A 64-year-old man was admitted because of pain and swelling of his right knee. His medical history consisted of type II diabetes mellitus controlled with diet, essential hypertension, and ischemic heart disease. In 2003 he began complaining of right knee arthralgias. Osteoarthritis was diagnosed and an intra-articular injection of long-acting methylprednisolone acetate controlled the pain. Because pain reoccurred, another injection of long-acting methylprednisolone acetate was administered to the knee on 5 July 2004, after aspiration of clear synovial fluid. The effect of the treatment was short-lived this time, and the knee pain reemerged within a couple of weeks. Sodium hyaluronate in a ready-to-use syringe was injected into the articular space on 15 August 2004. However, the pain worsened and the knee became swollen and red. A diagnostic tap

Received 1 December 2005; Accepted 12 February 2006
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of the knee was done 4 days later, and a purulent synovial fluid was obtained. Numerous polymorphonuclear leucocytes, but no crystals or organisms were seen on microscopic examination, and the culture was reported sterile. The erythrocyte sedimentation rate was 80 mm/h (Westergren) and C-reactive protein was 16.4 mg/dl. Arthroscopy was done, and a thorough rinsing of the intra-articular space was carried-out after synovial fluid was drawn for culture. Intravenous treatment with cefazolin and gentamicin was administered. Synovial fluid culture was again reported sterile, and the patient was discharged on oral antibiotics. Because he continued to suffer from his knee, the patient was readmitted on 19 September 2004. The knee fluid was cultured again, and was initially reported to be sterile. However, a few days later, the growth of a mold was observed. Because the laboratory technician recalled previously seeing a similar growth from synovial fluid, the patient's culture results were reviewed and it was noted that a mold was observed on three different occasions. However, the mold in the first two cultures had been initially dismissed as a contaminant. Empiric intravenous treatment with amphotericin B deoxycholate, 1 mg/kg per day, was administered for 6 weeks. After habitual adverse-effects (chills and fever, hypokalemia) were controlled, the patient received most of the treatment in an ambulatory setting. Pain and signs of inflammation regressed, and CRP decreased to 1.9 mg/dl. Repeat articular taps, at the end of the treatment and 2 months post-treatment, were sterile for both bacteria and fungi. Fourteen months post-treatment the patient was doing well.

The patient denied receiving any other injections, intravenously or intracavernously. The latter possibility was evoked because of an outbreak of systemic *P. curvatum* infection due to intra-cavernous penile injections occurred in the Tel-Aviv area, Israel, in 2002 [4]. Our patient's name did not appear on the lists of the sexual dysfunction clinic attended by the outbreak patients, as verified through the outbreak investigation. Evaluation for systemic infection was negative; his body temperature was normal throughout the follow-up period (except for an episode of amphotericin-associated fever), no heart murmurs were present, ophthalmologic examination was negative for endophthalmitis, and blood cultures were sterile.

Microbiology

Blood culture bottles (BD Bactec Plus+ Aerobic and BD Bactec Plus+ Anaerobic, Bacton, Dickinson and Co., Sparks, MD, USA) inoculated with synovial fluid

were monitored with the BACTEC 9240 system (Bacton, Dickinson and Co.). The first isolate (collected on 15 August) grew after 9 days of incubation, while subsequent cultures were positive after 4 days. The isolates had the appearance of yeasts on Gram-stained smears prepared from a portion of colonies in the blood culture bottles. Subculture onto Sabouraud dextrose agars incubated at 24 to 25°C demonstrated the characteristic appearance of a mold. Initially, on the basis of the yellowish-white colony and the production of long tapering phialides, the isolate was identified tentatively as an *Acremonium* species.

A ready-to-use syringe containing sodium hyaluronate was obtained from the patient for culture. To culture the fluid in the syringe, the entire contents were filtered through a 0.2 µm pore-size filter (Schleicher & Schuell, Dassel, Germany). The filter was placed on Emmons' modified Sabouraud glucose agar supplemented with 50 mg of chloramphenicol and 5 mg of gentamicin per liter. No growth was observed after incubation for a week at 35°C. The vial from which the corticosteroid was drawn was not available for culture.

Two isolates (collected on 21 August and 19 September) were referred to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio (UTHSCSA), and accessioned into their stock collection as UTHSC 04-3280 and 04-3281. Isolates were examined on potato flakes agar (prepared in-house) at 25°C for morphologic features [1]. Both isolates were identical and after 3 weeks incubation displayed flat, grayish-yellow colonies growing in concentric rings, measuring approximately 30 mm in diameter, and producing variously-sized, scattered sporodochial areas throughout the cultures. These sporodochial areas were cream-colored and mucoid centrally. Microscopic features included numerous and complex fascicles (bundles of hyphae), long slender phialides with basal septa (as seen in *Acremonium* species), and short adelophialides lacking basal septa (Fig. 1), both bearing aggregates of curved conidia at their apices. Also evident were numerous chlamydiconidia (Fig. 1), occurring either directly on the hyphae (sessile) or on short stalks. Young sporodochia were seen as microscopic aggregates of phialides. Numerous coils composed of long septate-like structures bearing conidia were also present. Based upon these features, the isolates were identified as *P. curvatum*, and were identical, morphologically, to those seen from the systemic *P. curvatum* infections occurring in Israel in 2002 as a result of intra-cavernous penile injections with contaminated fluids [4].

Retrospective antifungal susceptibility studies performed according to the previously published National

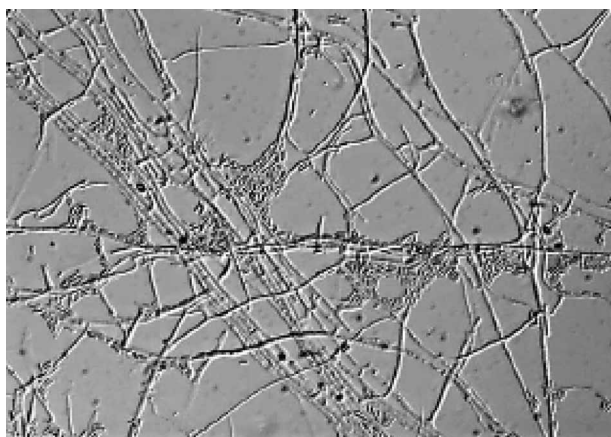


Fig. 1 Seen here are fasciculate hyphae (hyphae in bundles), short adelophialides (phialides not delimited by a basal septum (thin arrows), and chlamydoconidia (large arrow). Nomarski optics, $\times 950$.

Committee for Clinical Laboratory Standards M38-A methodology for filamentous fungi [5] revealed that the isolates also had susceptibility patterns consistent with those seen in the US hemodialysis cases and the other Israeli isolates. Based upon achievable drug level concentrations, as there are no defined breakpoints, isolates appeared resistant to amphotericin B (Bristol-Myers Squibb, Princeton, NJ, USA) and 5-fluorocytosine (Roche Laboratories, Nutley, NJ, USA) with 48 h minimum inhibitory concentrations (MIC) of 2 and >64 , respectively, and to caspofungin (Merck & Co., Inc., West Point, PA, USA) with an minimum effective concentration (MEC) of >16 $\mu\text{g/ml}$ [6]. Isolates appeared susceptible to itraconazole (Janssen Research Foundation, Beerse, Belgium) and posaconazole (Schering-Plough, Kenilworth, NJ, USA) with MICs of 0.125 and 0.03 $\mu\text{g/ml}$, respectively. The fluconazole (Pfizer, Inc., New York, NY, USA) MIC at 32 $\mu\text{g/ml}$ suggested potential efficacy with high dose therapy.

Discussion

Our patient developed a localized *Phialemonium* infection associated most probably with intra-articular injection of a corticosteroid. In another case of osteo-articular infection, *P. obovatum* was cultured from a tissue sample in a patient with lumbar osteomyelitis/diskitis. The authors have suggested that the mold was introduced by an injection done during radiological studies performed to investigate the patient's chronic back pain. He was otherwise healthy, and antifungal therapy had not been instituted [7]. A few cases of arthritis associated with other fungal species following intra-articular injections or needle aspiration have been

reported in the literature. *Candida* arthritis of the knee after corticosteroids injections was reported in seven patients, following needle aspiration in two cases (reviewed by E. Cuende *et al.* [8]), and after repeated injections of saline in one patient [9]. A case of *Exophiala* (*Wangiella*) *dermatitidis* phaeohyphomycosis in a patient with long-standing rheumatoid arthritis was associated with intra-articular corticosteroid injection [10]. More recently, a case of *E. dermatitidis* sacroiliitis was described as part of an outbreak caused by contaminated injectable corticosteroids prepared by a compounding pharmacy [11]. We share the experience of others regarding the ease of growth of *Phialemonium* in blood culture bottles, and the possibility of falsely identifying the organism as a yeast based on Gram-stained smears obtained from blood culture bottles [1]. Because the infection responded to amphotericin B administration well before the mold was identified as *P. curvatum*, and systemic infection was ruled-out, we elected to follow the patient without consolidating the treatment with another, 'more appropriate', antifungal agent.

Unfamiliar fungal isolates are frequently mistaken for environmental contaminants. The inclination to initially dismiss *Phialemonium* as a contaminant, as was the case with our patient, is exemplified in several reports [1,2,4,12]. Clinicians and microbiologists alike should be aware of the pathogenic significance of *Phialemonium* species when isolated from normally sterile sites in a suitable clinical setting.

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