Phialophora verrucosa as a Cause of Deep Infection Following Total Knee Arthroplasty

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Abstract

Deep joint infection is one of the most feared complications following total joint replacement. Prompt diagnosis and treatment with 2-staged revision is currently the gold standard for treatment. We report a case of a chronic infection following total knee replacement caused by *Phialophora verrucosa*, a form of dematiaceous fungus. The patient was treated with an antibiotic spacer and a course of oral anti-fungal agents. To our knowledge, there have been no reported cases of *P verrucosa* as a cause of infection in hip or knee arthroplasty.

Infection following total joint replacement is one of the most feared complications. Gram-positive bacteria such as *Staphylococcus aureus*, coagulase-negative Staphylococci, or *Propionibacterium acnes* are the most common culprits.[1] Joint infections following arthroplasty is a major cause of morbidity and place a great burden on the healthcare system. Infection rates in immunocompromised individuals and patients undergoing revision surgeries are higher than in immunocompetent patients undergoing primary total joint arthroplasty. While gram-positive bacteria are the most common causative agents, gram-negative bacteria and fungi have been isolated from cultures in cases of prosthetic joint infection.[2]

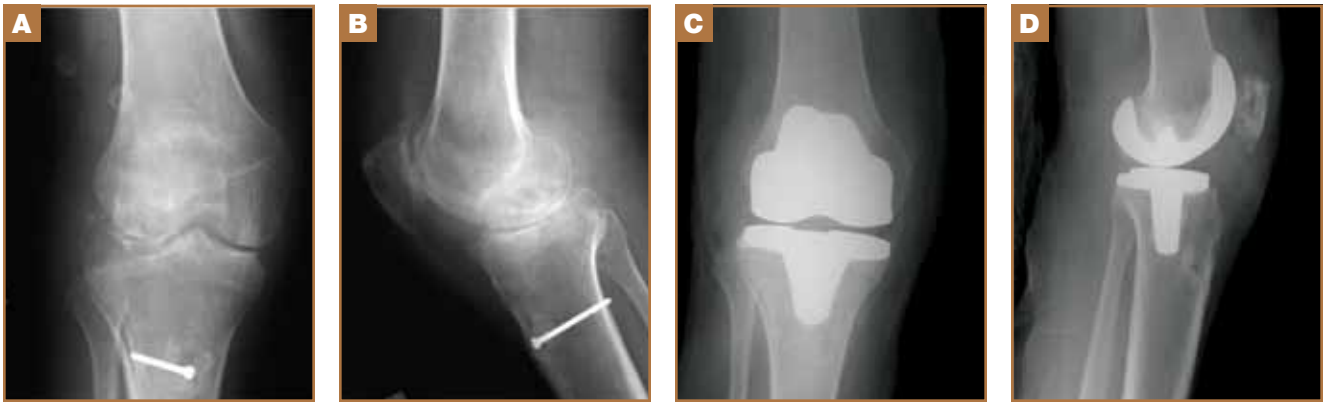
We present a case of dematiaceous fungus, *Phialophora verrucosa*, as the cause of an indolent chronic infection. To our knowledge there have been no reported cases of this organism in periprosthetic joint infections. The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 56-year-old healthy male underwent total knee arthroplasty in July of 2009 for posttraumatic osteoarthritis. His preoperative radiographs can be seen in **Figures 1A** and **1B**. He originally underwent anterior cruciate ligament repair as a teenager without any complications. In 2007, he had medial meniscus repair during which time he had a massive pulmonary embolism; the patient has been on warfarin ever since. Six months after the total knee replacement, he developed swelling and drainage over the superolateral aspect of his knee. At that time he had been afebrile, with normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell count. His knee was not warm or erythematous. Radiographs from this visit can be seen in **Figures 1C** and **1D**.

The patient had a clinical picture inconsistent with in-

Figure 1. Pre-arthroplasty AP (A) and lateral views (B) of the patient's knee showing posttraumatic arthritis. Radiographs (C, D) of the patient's 6 month follow-up visit; he developed drainage from his knee despite normal inflammatory markers.



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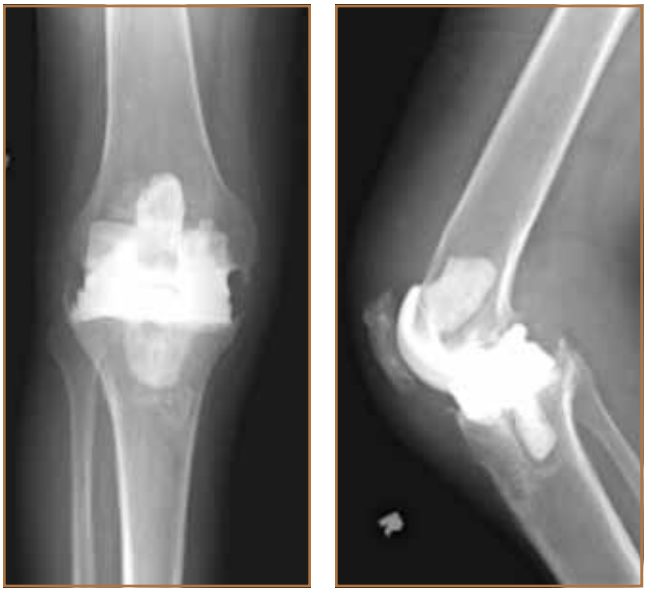

Figure 2. Radiographs of the patient's right knee after implantation of an antibiotic spacer.

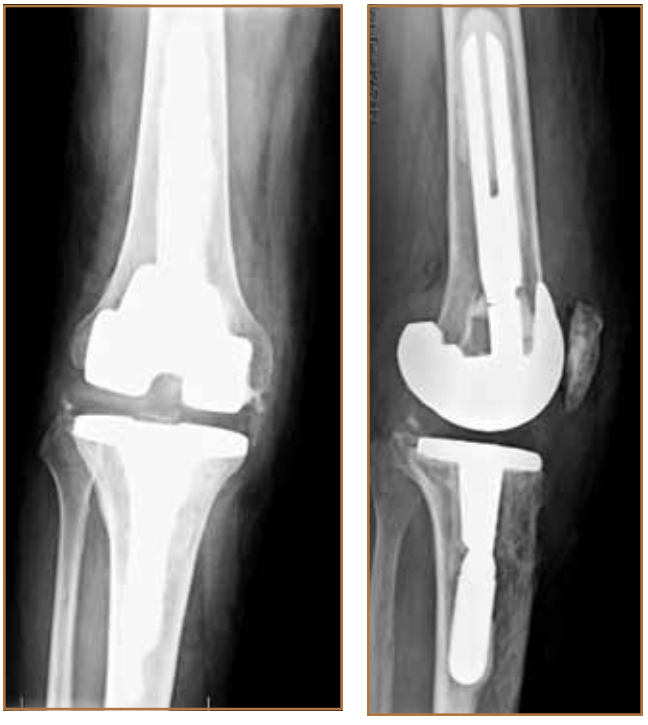

Figure 3. Radiographs of the patient's right knee after revision total knee replacement.

fection. ESR and CRP were negative, and physical examination findings made the diagnosis of infection unlikely. We decided not to perform aspiration or start antibiotics. A diagnosis of retinacular herniation with synovial sinus was made and the patient underwent synovectomy, debridement, and retinacular repair with removal of sinus tract. Frozen section was negative for acute inflammation at the time of surgery; cultures were taken for aerobic, anaerobic, fungal, and acid-fast bacilli. No growth was observed. The patient did well postoperatively until the episode re-occurred 6 months postoperatively. The patient underwent the same procedure and once again intraoperative frozen section was negative for acute inflammation and cultures showed no growth, including fungal cultures held for 8 weeks.

Three months after the second procedure, the patient developed another draining sinus from the superolateral aspect of his knee. His CRP and white blood cell count were within normal limits; ESR was slightly elevated. Range of motion was not limited by pain and he was able to ambulate without difficulty. He remained afebrile and his knee was not warm or erythematous. The decision was made to perform another debridement and retinacular repair. Antibiotics were not started prior to surgical intervention. At the time of surgery purulent material was found coming from the tract and connected with the joint and along the hamstring tendons. Frozen section was sent and once again found to be negative for inflammation. The prosthesis was found to be mostly well-fixed with a few areas of focal disruption of the bone cement interface. Despite prior negative frozen section and cultures, the nature of the intra-articular fluid and the focal areas of loosening lead to a high clinical suspicion for infection and we proceeded with irrigation, debridement, and explantation of the prosthesis with implant of cement spacer impregnated with gentamycin. Three sets of 3 intraoperative cultures were taken at the time for a total of 9 cultures. The tibia and femur were well fixed, but once removed were found to have fibrous tissue between the bone and implant in several locations. Postoperative radiographs can be seen in **Figure 2**. The patient was administered intravenous vancomycin as recommended by the infectious disease consult and discharged home with a plan for 6 weeks of therapy.

Intraoperative cultures remained negative until 16 days postoperatively, at which point *P verrucosa* was isolated from the fungal cultures; hyphae and conidia of the mold were at first mistaken for yeast. Cultures were positive for *P verrucosa* in 6 out of 9 cultures. Vancomycin therapy was discontinued and the patient was administered a 6-week course of oral voriconazole based on previous publications. This infection was reported to the US Department of Health who confirmed the culture results and ultimately searched the patient's home; the same fungus was isolated from the patient's kitchen. Based on the 6 positive cultures collected and identification of the source of the fungus in the patient's apartment, both we, and the US Department of Health, felt that this was a true infection and not a plate contaminant.

Due to the indolent course of this infection, the patient received 6 weeks of oral antifungal medication and was observed for an additional 3 months after discontinuation of the therapy, to make sure that there was no recurrence before re-implantation with a total knee prosthesis. Throughout this time, there was no recurrence of a draining sinus. The patient's inflammatory markers were within normal limits the entire postoperative period. The patient remained pain

free and without signs of infection.

An aspiration of the knee was considered prior to re-implantation, however given the excellent clinical course, normal inflammatory markers, and culture specific antifungal regimen, we decided that it was not necessary, and proceeded with revision total knee arthroplasty. No sinus tract was noted at the time of re-implantation. The synovial fluid appeared normal and frozen section was negative for acute inflammation. The patient was not placed on any anti-fungal medication postoperatively.

It has now been 18 months since the last surgery and all cultures, including fungal, are negative; the final results were determined after 8 weeks of incubation. The patient is currently ambulating with a cane and all inflammatory markers are within normal limits. The wound is well healed and there are no clinical signs of sinus tract or infection. Final radiographs can be seen in **Figure 3**.

Discussion

P verrucosa is a type of dematiaceous fungus. It is a common pathogen in the chronic skin infection known as chromoblastomycosis. This disease is most commonly found in rural areas in tropical climates. The most important risk factor is exposure such as walking barefoot or working with ones hands. Cases are also often found in immunocompromised patients, patients with indwelling catheters, or patients on chronic suppressive antibiotics.[3,4] The patient in our case report was not immunocompromised, lived in a cold urban environment, and had no history of traveling to tropical locations. To our knowledge, there have been no reported cases of *P verrucosa* as a cause of prosthetic joint infection.

There have been case reports and case series of patients with other fungal infections involving total hip and total knee replacements. The most common causative agent in these reports is Candida, although Aspergillus has been reported as well. Treatment in most cases was similar to those in bacterial periprosthetic infection, with thorough debridement and 2-staged re-implantation once infection had been eradicated.[5-7] There are reports of successful fungal treatment with single stage revision and even without removal of the prosthesis.[8,9] Local antifungal therapy is not currently available, and most cases have reported success with antibiotic cement spacers followed by re-implantation at an average of 7 months.[10-12] Amphotericin B has been tested in bone-cement, and found that while it does not weaken the cement, the amount eluted was not clinically significant and could not be detected after one week.[13]

One multi-center review performed by Azzam and colleagues[2] discussed the difficulty in treating periprosthetic fungal infections. Guidelines for treatment have been poorly outlined and many infections in this report persisted despite thorough debridement, 2-staged procedures, and several months of appropriate antifungal therapy.[2] The appropriate duration of antifungal treatment has not been well established, compared with bacterial infections, where 6 weeks is the standard of care. The appropriate duration of antifungal treatment reported in the literature ranges from anywhere between 6 weeks to 6 months.[14] Regardless of the duration of treatment, a prolonged follow-up to monitor for signs of recurrence is indicated. One of the difficulties with our patient was timely diagnosis. It was challenging to formulate a diagnosis because of the patient's normal laboratory values—except one mildly elevated ESR—and overall clinical picture, all of which differed from a typical bacterial infection.

Periprosthetic fungal infections are often found in patients who are immunocompromised or have other risk factors for infection such as diabetes, tuberculosis, intravenous drug use, or indwelling catheters. With the increased use of immunocompromising agents in rheumatoid arthritis, it is reasonable to assume that the rate of fungal infections will be on the rise.[14] Our patient had none of these risk factors making the diagnosis even more challenging. In addition, it is unclear whether identifying the source of the patient's fungus is significant. We do not know if the mold was present prior to the infection or if drainage from his wound seeded the apartment. A potential future area of study would be to determine if living conditions or even colonization of patients' homes are risk factors for periprosthetic joint infections.

As the number of total joint replacements performed each year continues to rise, so too will likely the incidence of deep joint infections caused by atypical species. Treatment protocols for fungal infections need to be better established and local antifungal modalities created. Clinical suspicion must always be high for periprosthetic joint infections in spite of normal laboratory values and negative cultures. Fungal cultures should always be kept for a minimum of 4 weeks.

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Technetium TC 99m scans can be considered to identify loose prostheses, which may hint at possible infection, although when performed in the first several months after joint replacement is non-specific. Our case demonstrates that when suspicion for joint injection is high despite negative testing for common pathogens, atypical species should be considered causative until ruled out. Multiple cultures and samples are often needed to make the correct diagnosis. As the suspicion for periprosthetic infection in our patient was low, no aspirations were performed. To our knowledge, there are no standards for intra-articular fluid values. Future studies must be directed at determining the cell count and cell type found

in periprosthetic fungal infections as this may lead to earlier diagnosis and treatment.

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This paper will be judged for the Resident Writer's Award.