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Case report

Protothecal bursitis after simultaneous kidney/liver transplantation: a case report and review

I. Ramírez, J.F. Nieto-Ríos, C. Ocampo-Kohn, A. Aristizábal-Alzate, G. Zuluaga-Valencia, O. Muñoz Maya, J.C. Pérez. Protothecal bursitis after simultaneous kidney/liver transplantation: a case report and review.
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Abstract: Solid organ transplantation is an accepted therapy for end-stage diseases of the kidneys, liver, heart, and lungs. Unfortunately, transplantation is associated with infectious complications. Here, we present a case report of *Prototheca wickerhamii* olecranon bursitis and review all of the cases in solid organ transplant (SOT) recipients published in the literature to date. In our patient, the infection resolved with surgical therapy and limited antifungal therapy, and no symptoms have recurred over 24 months of follow-up. A review of the literature suggests that 50% of SOT recipients with *Prototheca* infection present with disseminated infection, and the overall mortality is 75%. More studies are required to determine the optimal management of protothecosis in this population.

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Case report

A 74-year-old man with a history of simultaneous liver/kidney transplantation presented in April 2012 with a 2-week history of an erythematous nodular lesion and limited range of motion of the right elbow. He reported swimming in the Caribbean Sea off the coast of San Andres Islands, Colombia, 4 weeks before the onset of symptoms but denied any recent trauma. He underwent a simultaneous liver and kidney transplant 4 years earlier, as a treatment for cryptogenic cirrhosis and diabetic nephropathy. The transplant was complicated by mild hepatic dysfunction 2 years later because of hepatic steatosis confirmed by liver biopsy. His maintenance immunosuppressive therapy was cyclosporine (100 mg/day), mycophenolate sodium (360 mg twice daily), and prednisone (10 mg/day).

On physical examination, the patient was afebrile, and his vital signs were stable. He had erythema, edema, fluctuation, and tenderness upon palpation of the right elbow (Fig. 1), with no other concomitant findings. The routine laboratory test results were within the normal limits, except for mild lymphopenia and thrombocytopenia: white blood cell count 6400/mm^3, polymorphonuclear leukocytes 81%, lymphocytes 9%, platelet count 137,000/mm^3, erythrocyte sedimentation rate 21 mm/h, C-reactive protein 1.8 mg/dL, and

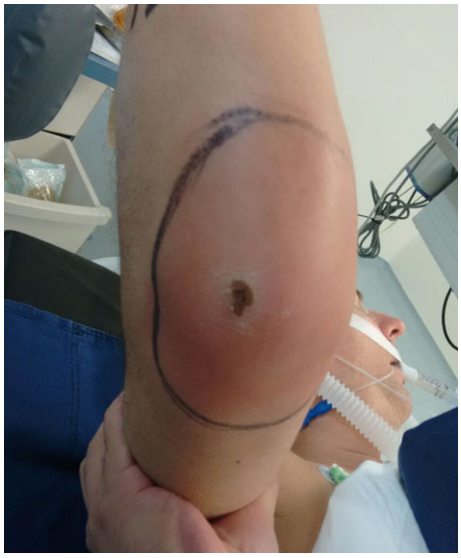

Fig. 1. Olecranon bursitis in right elbow.

normal liver function. His serum creatinine was 1.0 mg/dL, and his hemoglobin A1c was 6.1 mg%. The olecranon bursa was aspirated, and hematic fluid was obtained with 6250 white cells/mL and 897,500 red cells/mL. Bursectomy was performed.

Creamy colonies grew on chocolate, blood, and Sabouraud dextrose agars (Fig. 2). The wet mount preparation with lactophenol cotton blue showed spherical sporangia (4–8 μm in diameter) containing endospores with a symmetrical arrangement (Fig. 3). The microorganism was identified as *Prototheca wickerhamii* by the Vitek 2 system. The histologic examination demonstrated hyalinized fibroconnective tissue with moderate inflammatory infiltrate constituted of histiocytes, plasmocytes, eosinophils, and neutrophils, with occasional multinucleated giant cells and a zone of tissue necrosis. Spherical structures consistent with sporangium and containing sporangiospores were observed and stained positive with methenamine silver and periodic acid-Schiff (PAS) stains, suggesting *Prototheca* species (Fig. 4).

After surgical debridement and bursectomy, amphotericin B (AmB) deoxycholate treatment was initiated, but it was switched to voriconazole 48 h later because of renal dysfunction. However, 2 days after treatment with voriconazole was initiated, antifungal susceptibility testing showed resistance to azoles, and therefore, it was discontinued. The minimal inhibitory concentrations of the isolate were determined according to the Clinical and Laboratory Standards Institute guidelines and were as follows: fluconazole, >256 μg/mL; AmB, 0.125 μg/mL; itraconazole, >32 μg/mL; and voriconazole, >32 μg/mL. Over 24 months of follow-up, the patient showed no signs of local or systemic recurrence of infection.

Discussion

Prototheca is an achlorophyllous unicellular alga of low virulence of the genus *Chlorella* and is highly prevalent in the environment. It can be isolated from water, soil, and grass, and it colonizes the skin, fingernails, and the respiratory and gastrointestinal tracts of animals and humans (1). Protothecae are oval or spherical organisms that reproduce asexually by internal septation and cleavage, which produces between 2 and 20 sporangiospores. They differ from fungi in that they lack glucosamine in their cell walls. Protothecae are recognized pathogens in animals and cause bovine mastitis (2) and canine nasal dermatitis (3). Rarely, they cause infections in humans, which are mainly associated with trauma or opportunistic infections.

The genus *Prototheca* includes 5 generally accepted species: *Prototheca wickerhamii*, *Prototheca zopfii*, *Prototheca ulmea*, *Prototheca stagnora,* and *Prototheca blaschkeae*, plus a new species, *Prototheca cutis* sp. nov., that was recently identified (4). The species that are most frequently associated with human infections are *P. wickerhamii* and *P. zopfii*, the former of which is the most common agent in all types of human infections. Reports of *P. cutis* (dermatitis) (4) and *P. blaschkeae* (onychomycosis) (5) causing infection in humans have recently been published.

Protothecosis has been reported worldwide. In Latin America, 8 cases of cutaneous protothecosis have been reported. In Brazil, 4 cases of protothecosis caused by *P. wickerhamii* have been reported in immunocompetent patients and patients exposed to steroids (6–9). In Colombia, 4 cases of *Prototheca* species infection before our current case have been reported: 3 cases of cutaneous infection, 1 case of periungueal infection, and 1 case of olecranon bursitis (10, 11). Three of those patients acquired the infection locally, and the fourth patient was originally from Taipei, Taiwan. None of the previous cases occurred in the area where the current patient was exposed.

Although numerous cases of *Prototheca* infection in immunocompetent hosts with or without a history of trauma have been reported (6, 8, 12–20), immunosuppression is increasingly recognized as a risk factor, as it has been reported in patients with acquired immunodeficiency syndrome (AIDS) (21, 22), diabetes mellitus (23–25), chronic steroid use (26, 27), steroid and cyclosporine use for myasthenia gravis (28),

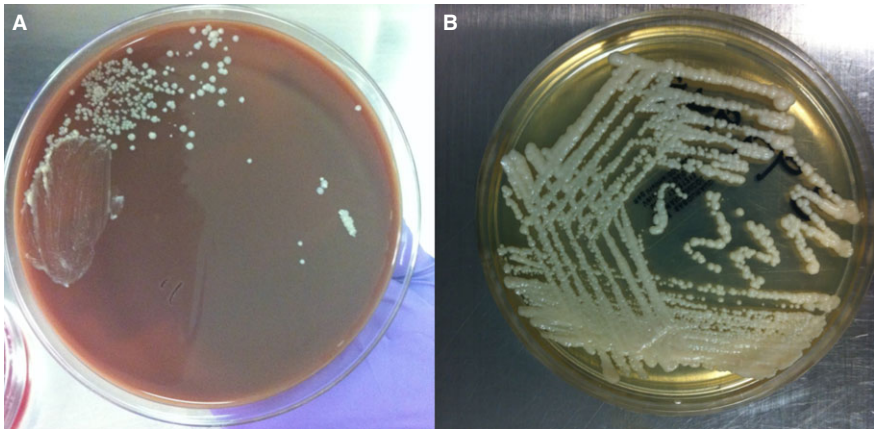

Fig. 2. Milky white yeast-like colonies are observed on blood agar plate after incubation at 35°C for 3 days (A) and Sabouraud agar after 7 days (B).

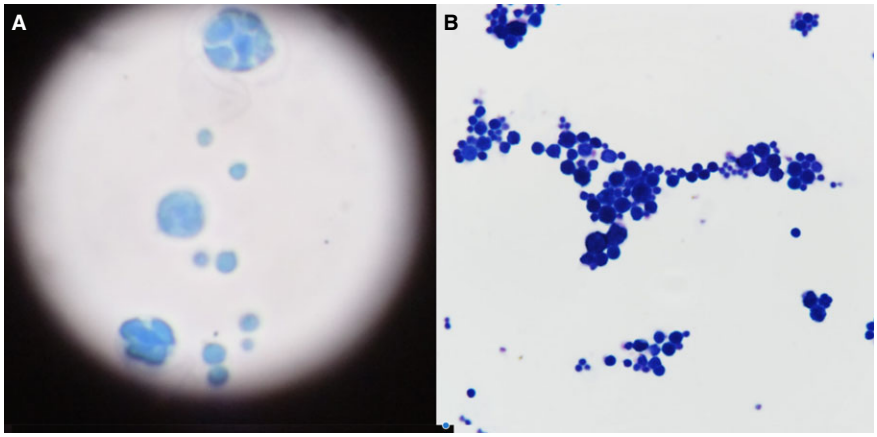

Fig. 3. Wet mount preparation of colony, stained with lactophenol cotton blue, showing spherical sporangia of different sizes, containing multiple endospores. Magnification ×400 (A), ×200 (B).

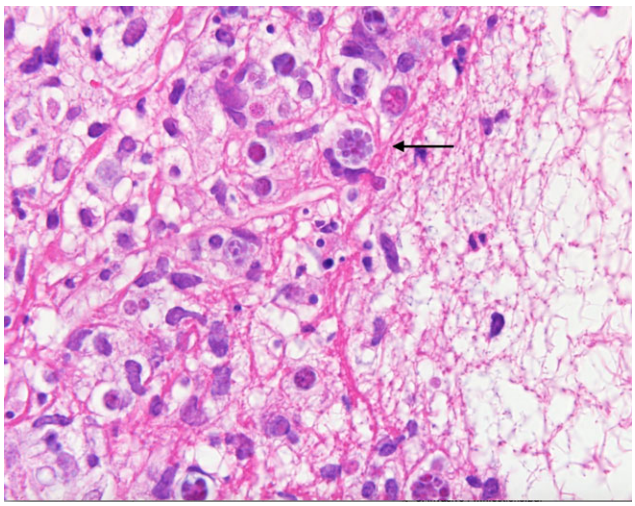

Fig. 4. Histopathological section of tissue sample obtained from the patient's bursa and stained with periodic acid-Schiff, showing spherical sporangia containing multiple endospores (arrow). Magnification ×400.

belimumab and rituximab use for systemic lupus erythematous (29, 30), chemotherapy for solid or hematologic malignancy (31–35), hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (36–50), and infliximab therapy for graft-versus-host disease after HSCT (38). A case of breakthrough protothecosis during long-term voriconazole therapy for pulmonary aspergillosis after HSCT was also reported (37). In our case, an immunocompromised patient without a history of trauma was exposed to salt water and presented with olecranon bursitis. We consider that his infection was acquired in the sea and was inoculated through skin breakdown from minimal trauma that had gone unnoticed.

The pathogenesis of *Prototheca* infection is unknown, but it has been hypothesized that direct skin inoculation occurs due to traumatized areas being exposed to contaminated sources. The incubation period is unknown, but based on case reports, it ranges from weeks to months (1).

As *Prototheca* species behave as opportunistic pathogens, it has been suggested that defects in cellular and

humoral immunity increase susceptibility to this infection. Previously, human neutrophils were shown *in vitro* to ingest and kill *P. wickerhamii*, and this process is facilitated by opsonins. Immunoglobulin-G antibodies specific for *P. wickerhamii* and serum opsonin have algicidal activity, which has been described in patients with hypogammaglobulinemia secondary to common variable immunodeficiency and the use of inhibitors of alpha tumor necrosis factor, the latter of which also favors the appearance of granulomatous infections, such as the infection in this case (51). *Prototheca* infections are uncommon in AIDS and neutropenic patients, which suggests that defects in natural killer (NK) cell activity favor these infections (52). The relationship with NK cell defects has not been clearly demonstrated, but in at least 1 case, suppressed NK cell activity was demonstrated before the initiation of therapy (52).

The spectrum of illness with *Prototheca* infection ranges from localized indolent skin and soft-tissue infection (66% of cases) and olecranon bursitis in immunocompetent patients (15%) (12, 53–58), to a devastating disseminated infection with algaemia and visceral infiltration (19% of cases) with high mortality in immunosuppressed hosts (24). At least 3 cases have been reported where the infection caused cholestatic hepatitis (30). Less frequent presentations are lymphadenitis (16) and urinary tract (59) and central nervous system (60) infections in immunocompetent hosts and peritonitis in patients undergoing peritoneal dialysis (61) and HSCT (62).

Among the 7 cases of olecranon bursitis reported, 3 patients had impaired immunity because of diabetes mellitus, chronic prednisone use, or metastatic cancer (12, 54, 57). In most cases, the diagnosis was made by culture and histology showing the presence of granulomas. In 4 cases, bursectomy alone was curative, and in the other 3 cases, antifungals, such as itraconazole or topical AmB, were administered (12, 53–58).

To date, 12 cases, including ours, have been reported in solid organ transplant (SOT) patients, 6 with localized infections and 6 with disseminated infections with algaemia. Interestingly, 50% of those patients were also diabetic. Infection was documented as early as 40 days and as late as 20 years after transplantation. The main source of acquisition was usually considered to be environmental, but infection has also been reported after long periods of hospitalization, indicating the possibility of nosocomial acquisition. The reported cases in SOT patients were as follows: 1 liver transplant (42), 1 lung transplant (50), 2 cardiac allografts (40, 41), 7 renal transplants (43–49) (Table 1), and 1 simultaneous liver/kidney transplant (in our current case report). In half of the cases, patients had coinfections with other microorganisms, such as pyogenic bacteria and yeasts, such as *Candida* species, which could be explained by skin breakdown serving as the portal of entry for more virulent pathogens. Those coinfections, in addition to coinfection with cytomegalovirus, reflect the net state of immunosuppression in these cases, which is always associated with a fatal outcome. Approximately 50% of *Prototheca* infections manifest as a localized (cutaneous) infection with secondary spread and disseminated disease (algaemia). The overall mortality is 75%, although death was directly attributed to protothecosis in only 6 of 9 cases. The high mortality rate could be the result of a delay in diagnosis owing to the lack of clinical suspicion and the subsequent delay in treatment, including reduction of immunosuppression (40, 42, 48). Antimicrobial susceptibility was reported in 4 cases, and all isolates were susceptible to AmB, with variable susceptibilities to itraconazole, voriconazole, and posaconazole. In our case, it is possible that our patient's net state of immunosuppression was not as profound as in previous cases, because the patient did not have other superinfections. That fact and early consultation with the appropriate subspecialties contributed to the favorable outcome in this case, despite the limited use of antifungal therapy.

The final diagnosis was made by culture or histopathology. Initially, algae may be confused with yeast in routine media and can be misidentified as *Candida* species (40). In addition, false-positive results for serum galactomannan have been reported (17). Culturing the organism on an appropriate medium, such as Sabouraud dextrose agar, is required to obtain a definitive diagnosis. Speciation is determined with the VITEK 2, API system, or matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (63). Upon histological examination, tissue necrosis and granulomas are frequently observed, but such changes can be absent (1, 64). Although *Prototheca* can be visualized with hematoxylin–eosin staining, the yield of PAS and methenamine silver stains is higher (65). The stained organisms usually demonstrate internal cleavage of the sporangia with endospores; in the absence of those features, the organisms may resemble fungi, such as *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, and *Pneumocystis jirovecii*. *Protothecae* are differentiated from *B. dermatitidis* and *C. neoformans* by their size, internal structure, and the absence of budding (65).

An increasing number of molecular techniques have successfully been used for diagnosis. Currently, rapid automated identification is possible with the availability

Protothecal infection in solid organ transplant recipients

Country Age/ Gender (Ref.)	Transplant/ comorbidity	Time since transplant	Infection	Immunosup-pression	Pathogen/ identification method	Coinfection	Pathology	Susceptibility testing MIC	Treatment	Outcome/ attributable
Australia 78/F (40)	Cardiac allograft DM CKD	15 years	Disseminated algaemia and soft tissue	CsA 20 mg/day MMF 1 gr/day PDN 7.5 mg/ day	*Prototheca wickerhamii* Blood cultures Vitek 2 26S rRNA gene	UTI: VRE	Necrosis and inflammatory infiltrate PAS	ICZ 1 mg/L, VCZ 0.5 mg/ L, PCZ 1 mg/ L, CSP 16 mg/L, AmB 0.25 mg/L	ICZ/AmB	Died/yes
United States 69/F (41)	Cardiac allograft DM	9 years	Disseminated algaemia	PDN 5 mg MMF 1 gr CsA 20 mg	*P. wickerhamii* Blood cultures Vitek 2	Fungemia *Candida glabrata*	–	NR	CSP	Died/yes
United States 61/M (42)	Liver DM	40 days	Disseminated algaemia, skin	TAC PDN MMF	*P. wickerhamii* Chocolate agar Vitek 2	Bacteremia: *Escherichia coli*, VRE CMV viremia	–	AmB 0.06 μg/ mL CSP 8 μg/mL, MCF >10 μg/ mL, VCZ 2 μg/mL	AmB	Died/yes
United States 30/M (43)	Kidney Post-transplant DM	2 years	Cutaneous	AZT 75 mg/day PDN 50 mg/day CFM, HALG	*P. wickerhamii*	Skin infection: *Candida albicans*	Necrotic areas inflammatory infiltrate, MS and PAS	NR	Tetracycline	Died/no
Malaysia 61/M (44)	Kidney Loss of allograft ESRD	20 years	Disseminated algaemia	None	*P. wickerhamii* Blood culture Sabouraud dextrose agar, Lactophenol cotton blue API 20C	None	–	AmB 0.094 μg/mL Resistant by E-test to ICZ, VCZ, CSP	None	Died/yes
United States 44/M (45)	Kidney Splenectomized	NR	Cutaneous	AZT PDN	*P. wickerhamii* API20C	Unknown	Chronic inflammatory infiltrate, granuloma, MS and PAS	NR	Excision and Tetracycline	Died/no
NR 45/M (46)	Kidney		Skin	NR	*P. wickerhamii*	Unknown	NR	NR	Amputation	Cure

Table 1 Continued

Country Age/ Gender (Ref.)	Transplant/ comorbidity	Time since transplant	Infection	Immunosup-pression	Pathogen/ identification method	Coinfection	Pathology	Susceptibility testing MIC	Treatment	Outcome/ attributable
NR 30/M (47)	Kidney	2 years	Cutaneous abscess	AZT PDN HALG	*P. wickerhamii*	*C. albicans*, *Proteus mirabilis*, *Klebsiella* species	NR	NR	Drainage, local GNT	Died/no
NR 48F (49)	Kidney CKD	NR	Skin, cellulitis	Steroids CFM	*P. wickerhamii*	Unknown	NR	NR	NR	NR
United States 59/F (50)	Lung	3 months	Disseminated algaemia	Unknown	*Prototheca* species	CMV viremia, *Serratia marcescens* pneumonia	–	NR	NR	Died/yes
United States 59/M (48)	Kidney DM Primary graft failure	4 months	Cutaneous algaemia	Plasmapheresis PDN 5 mg MMF AZT TAC	*P. wickerhamii* Blood culture, Sabouraud Lactophenol cotton blue, Vitek 2, PAS MALDI-TOF MS	None	NR	AmB 0.5 μg/mL VCZ 6 μg/mL	AmB	Died/yes
Colombia 74M (Present)	Kidney/liver DM	7 years	Olecranon bursitis	CsA 100 mg/day SMF 720 mg/day PDN 10 mg/day	*P. wickerhamii* Chocolate and Sabouraud dextrose agar, Lactophenol cotton blue, Vitek 2	None	Inflammatory infiltrate, multinucleated giant cells, necrotic tissue, MS and PAS stain	AmB 0.125 μg/mL ICZ >32 μg/mL VCZ >32 μg/mL	Bursectomy AmB withdrawal in 48 h	Cure Alive 48 months

MIC, minimum inhibitory concentration; F, female; DM, diabetes mellitus; CKD, chronic kidney disease; CsA, cyclosporine; MMF, mycophenolate mofetil; PDN, prednisone; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci; PAS, periodic acid-Schiff; ICZ, itraconazole; VCZ, voriconazole; PCZ, pozaconazole; CSP, caspofungin; AmB, amphotericin B; NR, not reported; M, male; TAC, tacrolimus; CMV, cytomegalovirus; MCF, mycophenolic acid; AZT, azathioprine; CFM, cyclophosphamide; HALG, horse antilymphocyte globulin; MS, methenamine silver; ESRD, end-stage renal disease; GNT, gentamicin; MALDI-TOF MS, matrix-assisted laser desorption ionization–time of flight mass spectrometry; SMF, sodium mycophenolate.

Table 1

of MALDI-TOF MS. This technique uses a fingerprint matching approach, which not only allows for the differentiation of *Prototheca* species but also for the differentiation of genotypes 1 and 2 (63), which is otherwise not always possible. API 20C or MALDI-TOF 18S rRNA and 28S rDNA sequencing have also been used successfully (4). The new strategy of coupling broad-range polymerase chain reaction (PCR) amplification to automated electrospray ionization mass spectrometry (PCR/ESI-MS) identifies the organism at the species level by measuring the masses of nucleotides from PCR amplicons (66).

Although various treatment regimens are used, the optimal therapy remains controversial, and AmB is still the mainstay therapy for immunocompromised patients. *Prototheca* species have approximately 4% ergosterol in the neutral lipid fraction of the cell membrane, a feature that is likely responsible for their susceptibility to AmB. In addition, the presence of free fatty acids is responsible for their susceptibility to azoles (67). Although voriconazole has been tested against isolates of *P. wickerhamii* with an MIC90 of $\leq$0.05 μg/mL, its efficacy should be supported by clinical experience (68). In some reported cases, voriconazole has been used alone (34, 69, 70) or in association with AmB (39) with good outcomes. Other antifungals, such as the echinocandins, have not been used because *Prototheca* lacks glucan in its cell wall.

Although antifungals, including topical or systemic griseofulvin and AmB, have been used (71), surgical resection can be curative for olecranon bursitis, even in the absence of antifungal therapy. Therefore, removal of the source of infection is recommended whenever possible to ensure a successful outcome. This management strategy is probably applicable only for immunocompetent patients and cannot be extrapolated to all immunosuppressed patients owing to the high rate of secondary dissemination with fatal outcomes; therefore, aggressive initial antifungal therapy should be given until the extent of infection is defined.

Conclusion

Protothecosis is an unusual infection even in immunosuppressed hosts, for whom it is considered an emerging infectious disease. In SOT patients, it behaves as an opportunistic pathogen with high mortality, and it can present at any time in the post-transplant period. The main clinical presentation is disseminated disease, which is often accompanied by bacterial, viral, or fungal coinfection. Currently, molecular approaches are widely used and have potential to complement phenotypic identification, allowing a prompt and accurate diagnosis. The best therapy is still controversial, and treatment success depends on the net state of immunosuppression, the administration of antifungals, and surgery whenever it is possible.

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