

Case report

***Mycobacterium marinum* infections in transplant recipients: case report and review of the literature**

T.K. Pandian, P.J. Deziel, C.C. Otley, A.J. Eid, R.R. Razonable.
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Abstract: Infections due to *Mycobacterium marinum* are rarely encountered following organ and tissue transplantation. Herein, we report a case of *M. marinum* infection in a kidney and pancreas transplant recipient who manifested clinically with multiple locally spreading sporotrichoid-like cutaneous nodules in his left forearm. In order to provide a general overview of post-transplant *M. marinum* infections, we reviewed and summarized all previously reported cases of this infection that occurred after transplantation. Including our index case, all 6 cases presented with multiple cutaneous and subcutaneous nodules that had spread locally in the involved extremity. One patient had lesions located in non-contiguous body sites suggesting either systemic dissemination or multiple sites of inoculation. In all but 1 patient, the cutaneous nodules appeared in an ascending pattern and following exposure to fish tanks or after contact with the marine environment. The diagnosis of *M. marinum* infection was suspected on clinical grounds and confirmed by mycobacterial culture. Treatment consisted of at least 2 active antibiotics (such as rifamycins, ethambutol, tetracyclines, or macrolides) for 4–9 months, resulting in clinical cure or improvement. Relapse was observed in 1 patient despite completing 6 months of antibiotic therapy. One patient had surgical excision of the lesions. In conclusion, *M. marinum* should be considered as the cause of cutaneous and subcutaneous nodules in transplant recipients, particularly in the context of fish tank or marine exposure. Compared with the immunocompetent hosts, *M. marinum* infection may have a more aggressive clinical course after transplantation, and may require a longer duration of antibiotic treatment. Early diagnosis and treatment may prevent local spread and potential systemic dissemination.

**T.K. Pandian¹, P.J. Deziel², C.C. Otley³,
 A.J. Eid⁴, R.R. Razonable^{2,4}**

¹Mayo Medical School, ²William J von Liebig Transplant Center, ³Department of Dermatology, ⁴Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

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Correspondence to:
 Raymund R. Razonable, MD, Division of Infectious Diseases,
 Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
 Tel: + 1 507 284 3747
 Fax: + 1 507 255 7767
 E-mail: Razonable.raymund@mayo.edu

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Individuals who have received organ and tissue transplants are predisposed to develop infections due to typical and opportunistic pathogens, including *Mycobacterium* species (1). The incidence of *Mycobacterium* sp. infections have varied depending on exposure history and area of endemicity. *Mycobacterium tuberculosis* has been reported to occur in 0.35–15% of solid organ transplant recipients worldwide, with higher rates occurring in highly endemic areas (2), whereas non-tuberculous mycobacterial infections have been observed less frequently, at an estimated incidence of 0.16–2.8% of transplant recipients in the United States, with most cases attributed to *Mycobacterium avium-intracellulare* complex (3). Although mycobacterial infec-

tions are uncommon, they pose a significant clinical risk to transplant recipients because of their aggressive clinical course and the complexities of the antibiotic regimens used for their treatment (3). Furthermore, rare infections such as those caused by non-tuberculous mycobacteria pose a clinical challenge to physicians because of the lack of consensus regarding their optimal treatment in the context of persistent immunosuppression.

Mycobacterium marinum, a waterborne non-tuberculous mycobacteria, has rarely been reported as a pathogen after transplantation (4–8). In this article, we describe what we believe is the sixth reported case of post-transplant *M. marinum* infection. To characterize the clinical course

of this infection in transplant recipients, we summarized all previously reported cases and our review indicates many commonalities in their clinical course and treatment, and thus, this article is aimed at providing a general overview of the clinical presentation, treatment, and outcomes of *M. marinum* infections after transplantation.

Case report

In August 2007, a 37-year-old diabetic male kidney transplant recipient presented to the Transplant Infectious Disease Clinic with several sporotrichoid-like erythematous tender nodules that developed in his left forearm during the previous month (Fig. 1A and B). Five years earlier, in February 2002, he received his first kidney transplant from a living unrelated donor, and this was followed 5 months later by a pancreas transplant. He was cytomegalovirus (CMV) seronegative before both kidney and pancreas transplants and thus, he received two 3-month courses of valganciclovir prophylaxis, which ended in September 2002. Two months later, in November 2002, he developed delayed-onset primary tissue-invasive CMV disease characterized by recurrent episodes of CMV esophagitis. In June 2003, his kidney allograft failed because of BK virus-associated nephropathy. In January 2006, he received a second

kidney allograft from a deceased donor. He received induction immunosuppression with anti-thymocyte globulin and was maintained on a triple regimen of tacrolimus, mycophenolate mofetil, and prednisone.

Four weeks before his visit to the Transplant Infectious Disease Clinic, he observed an ulcer on the ulnar side of his distal left forearm (Fig. 1A). The ulcer evolved to develop purulence that required incision and drainage by his local physician. Specimens obtained from this procedure were sent for histopathology, which was reported as an abscess with inflammation and granulation tissue. Routine bacterial culture of the biopsy specimen was negative. The patient received an empiric 10-day course of moxifloxacin, without clinical improvement. Over the next month, he observed the development of several erythematous tender cutaneous and subcutaneous nodules along the lateral aspect of his left forearm (Fig. 1B). These crops of similar-looking lesions appeared progressively in an ascending pattern and without any associated systemic symptoms.

On physical examination, the skin nodules along his left forearm were firm, mildly tender, and erythematous, characteristic of a classic sporotrichoid presentation. On further review, the patient reported contact with soil and plant material as he was mowing his lawn during the summer. He also recalled contact with dogs that had been rolling in the dirt. Earlier in the summer, he cleaned a saltwater aquarium tank but denied having any skin lacerations,

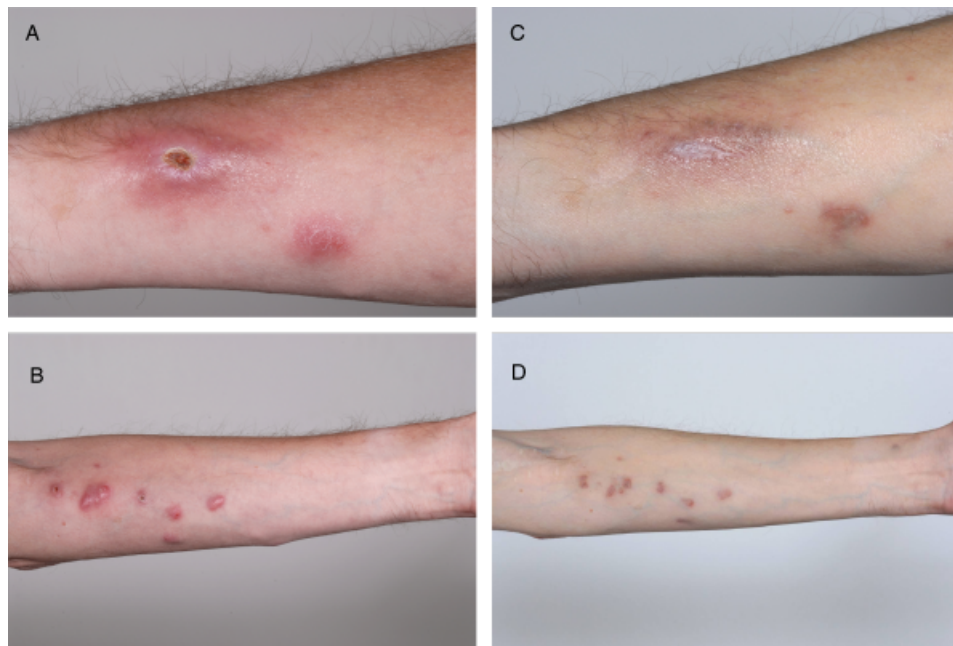


Fig. 1. Sporotrichoid-like lesions due to *Mycobacterium marinum* in the left forearm of a kidney and pancreas transplant recipient. (A) Initial ulcerated lesion; (B) Ascending spread of the lesions before the initiation of effective antibiotic therapy; (C) The initial ulcerated lesion following 4 months of clarithromycin and rifabutin therapy; (D) Scarring of the nodules in the left forearm after 4 months of clarithromycin and rifabutin therapy.

punctures, or scrapes. A skin punch biopsy of the left forearm showed abscess with mixed mononuclear and polymorphonuclear leukocytic infiltrates and inflamed granulation tissue. No fungal elements or acid-fast bacilli were observed on histopathology. Because of the sporotrichoid nature of his lesions, the patient was started empirically on oral itraconazole, 100 mg twice daily. Serology for *Sporothrix schenckii*, *Histoplasma capsulatum*, and *Cryptococcus neoformans* were negative. Three weeks later, the mycobacterial cultures from 2 separate biopsy specimens yielded the growth of *M. marinum*. The organism was susceptible to amikacin, clarithromycin, ethambutol, linezolid, moxifloxacin, rifabutin, rifampin, and trimethoprim-sulfamethoxazole; it had intermediate susceptibility to minocycline and was resistant to ciprofloxacin (Mycobacteria/Nocardia Research Laboratory, The University of Texas Health Center, Tyler, Texas, USA). Hence, itraconazole was discontinued and the patient was commenced on clarithromycin, 500 mg orally twice daily, and rifabutin, 300 mg orally once daily. Except for mild nausea early during the course of therapy, the patient tolerated the medications well. Clinical follow-up at 4 months after the initiation of combined therapy showed a remarkable reduction in the diameter and flattening of the skin lesions (Fig. 1C and D). At the time of this report, he had completed 4 months of clarithromycin and rifabutin therapy, with the plan of continuing the combined therapy for 2 months after complete resolution of the skin lesions.

Review of the literature

A search of the medical literature, using various combinations of the terms 'transplantation,' 'solid organ transplantation,' 'bone marrow transplantation,' 'stem cell transplantation,' 'kidney transplantation,' 'liver transplantation,' 'heart transplantation,' 'lung transplantation,' 'mycobacterium,' and '*Mycobacterium marinum*' yielded between 0 and 9 original articles per search. After a secondary search using the references listed in original articles, we identified a total of 5 unique cases of *M. marinum* infections after transplantation (4–8). Only culture-defined cases of *M. marinum* infections that occurred after any type of transplantation were included in this analysis. Hence, including our index case, there are now a total of 6 cases with *M. marinum* infections after transplantation. The details of the clinical presentation, treatment, and outcome of these cases are described in Table 1. The mean age of the 6 patients was 44 years (range, 30–52). There were similar proportions between male and female patients. All except 1 patient (Patient no. 4; a lung transplant recipient) had received a kidney with or without pancreas transplant.

Three were recipients of multiple organ transplants. No patient had received liver, heart, hematopoietic stem cell, or bone marrow transplantation.

The mean time for the onset of *M. marinum* skin infection was 3.7 years (range, 1–8) after the most recent transplant procedure. The clinical presentation was similar among the 6 reported cases, with erythematous tender cutaneous nodules measuring 1–3 cm in diameter. In some of the cases, the lesions progressed to develop ulceration. There was a sporotrichoid-like and lymphangitic characteristic to these lesions. With the exception of 1 patient who had lesions in non-contiguous sites (Patient no. 5) (8), the skin nodules were localized only to a single extremity. The upper extremity was involved more often than the lower extremity. The crop of lesions typically spread locally and proximally in an ascending manner. There was no documented systemic dissemination in 1 patient whose lesions remained localized to the same extremity for 12 months before diagnosis and treatment (Patient no. 4) (7). On the other hand, 1 patient (Patient no. 5) (8) had lesions located in non-contiguous sites (arms, leg, and left foot), suggesting possible disseminated disease or simultaneous inoculation at multiple sites. In all except this patient with multifocal non-contiguous lesions (Patient no. 5) (8), a clear exposure to fish tank and marine environment was reported (4–7). In particular, patients typically reported cleaning fish tanks (Patients no. 1, 4, and 6) (6, 7) and 1 patient reported using the fingers to check the water temperature of the aquarium (Patient no. 2) (4). One patient reported fishing and swimming in Florida before the onset of the skin nodules (Patient no. 3) (5).

In all 6 cases, the diagnosis was confirmed when *M. marinum* was isolated on mycobacterial culture from tissue specimens obtained from the skin nodules. Routine bacterial cultures were reported as negative. Histologically, the lesions showed non-caseating granuloma, granulomatous inflammation, and suppuration. In 2 cases, the mycobacterial culture of specimens (aquarium, water, or fish) obtained from the environment where the exposure occurred yielded *M. marinum* (Patients no. 1 and 2).

Because of clinical suspicion of either a bacterial or fungal skin infection, the patients typically received short-course empiric therapy with amoxicillin-clavulanic acid, moxifloxacin, doxycycline, or itraconazole before the diagnosis and treatment of *M. marinum* infection. Non-resolution or progression of skin lesions occurred during therapy with these drugs. Local spread and progression of skin lesions were halted when patients were commenced on combinations of effective antimicrobial therapy. The details of the definitive antibiotic therapy are given in Table 1. Ethambutol was used in 5 of 6 cases (5–8), in combination with rifampin (Patients no. 1, 2, and 5) (4, 6, 8), ciprofloxacin (Patient no. 2) (5), azithromycin (Patient no. 4) (7), or

Clinical characteristics and outcomes of 6 transplant patients with *Mycobacterium marinum* infections

Patient no. (Reference)	Age/sex	Transplant/immunosuppression	Exposure	Clinical and pathologic findings	Treatment	Outcome
1 (6)	30/M	DDKTx Azathioprine, prednisone	Fish tank	Onset: 3 years post Tx Gross: Linear, tender, ulcerated nodules on extremities	EMB 1 g/day + RIF 600 mg/day Recurrence after RIF was stopped Re-treated with EMB + TMP-SMX	Not reported
2 (4)	52/F	DDKTx x2 Cyclosporine, azathioprine	Fish tank	Onset: 1.5 years after last transplant Gross: Sporotrichoid nodules on the lateral aspect of right fifth digit, hand, forearm, and arm Histology: Dense lymphocytic infiltrates and polymorphonuclear cells in deep dermis	DOC 400 mg/day but progressed RIF 600 mg/day + EMB 800 mg/day for 3 months	Cure
3 (5)	48/M	DDKTx Cyclosporine, MMF, prednisone	Fishing, swimming	Onset: 1 year post Tx Gross: Linear, tender, ulcerated, 1–2 cm nodules on left forearm Histology: Granulomatous inflammation and fibrosis with suppuration	EMB 1.2 g/day + CIP 750 mg b.i.d. for 6 months Recurrence treated with 3 additional months of EMB + CIP	Cure
4 (7)	52/F	Lung transplant Cyclosporine, azathioprine, prednisone	Fish tank	Onset: 2.5 years post Tx Gross: Tender, firm, <1.5-cm nodules on right hand and forearm Histology: Non-caseating granulomatous inflammation and fibrosis	EMB 800 mg/day + AZT 500 mg/day + MCL 100 mg b.i.d. for 6 months; surgical excision of lesions (because of tissue irritation)	Cure
5 (8)	45/F	SPKTx Cyclosporine, azathioprine, prednisone	Not reported	Onset: 8 years post Tx Gross: Ulcerated tender 3-cm nodules on arms, shanks, and left foot Histology: Necrotic center with peripheral granulomatous inflammation	EMB + RIF + INH; then Protionamide was added for total antibiotic duration of 4 months	Cure: the patient died of cerebral hemorrhage
6 (Present case)	37/M	LUDKTx, PAKTx, DDKTx Tacrolimus, MMF, prednisone	Fish tank	Onset: 1.5 years after last Tx Gross: Erythematous, tender, ulcerative nodules in ascending pattern on left forearm Histology: Abscess with granulomatous inflammation	CLR 500 mg b.i.d. + RFB 300 mg/day	Improved at 4 months of ongoing therapy

M, male; F, female; DDKTx, deceased donor kidney transplant; SPKTx, simultaneous kidney and pancreas transplant; LUDKTx, living unrelated donor kidney transplant; PAKTx, pancreas after kidney transplant; EMB, ethambutol; RIF, rifampin; TMP-SMX, trimethoprim-sulfamethoxazole; DOC, doxycycline; CIP, ciprofloxacin; AZT, azathioprine; MCL, minocycline; INH, isoniazid; CLR, clarithromycin; RFB, rifabutin; MMF, mycophenolate mofetil.

Table 1

minocycline (Patient no. 4) (7). In 1 patient (Patient no. 5) (8), protionamide was added to the regimen when the skin nodules failed to completely regress despite 4 months of rifampin, ethambutol, and isoniazid therapy. One patient (Patient no. 1) developed ulceration of the skin lesions when the patient discontinued rifampin from the ethambutol–

rifampin combination therapy (6); the addition of trimethoprim–sulfamethoxazole led to clinical improvement.

The duration of antibiotic treatment in the 5 previously reported cases ranged from 3 to 6 months; however, in 1 patient (Patient no. 3), recurrence of the skin lesion occurred after the completion of 6 months of ethambutol

and ciprofloxacin therapy (5). Therefore, this patient (Patient no. 3) received additional treatment with ethambutol and ciprofloxacin for 3 months leading to the complete resolution of the skin lesions with no further clinical relapse.

Discussion

Mycobacterium marinum was first recognized (as *M. balnei*) in 1926 by Aronson, who discovered the organism as causing the death of fish in the Philadelphia Aquarium (9). In 1954, Norden and Linnel first recognized *M. marinum* as a cause of clinical disease in humans when they reported this organism as causing infection in 80 individuals who had used the same swimming pool (10). Because of the association of *M. marinum* with the aquatic environment, 'swimming pool granuloma' and 'fish tank granuloma' are common phrases used to describe this infection (11). The first case of *M. marinum* infection after transplantation was first reported by Gombert et al. in 1981 (6). Since then, there have only been a total of 5 cases reported in transplant recipients (4–8). To our knowledge, we now describe the sixth case of *M. marinum* infection in the transplant population. Summarizing the clinical information of all these cases, this review indicates that *M. marinum* infection after transplantation is manifested predominantly as multiple locally spreading sporotrichoid-like cutaneous and subcutaneous nodules. The non-contiguous multifocal nature of the lesions in 1 case suggests the potential for spread beyond the site of inoculation (8).

Although the literature on *M. marinum* infections in transplant recipients is not extensive, there appears to be commonalities to the clinical presentation, histology, treatment, and outcome of all the 6 cases described. Similar to *M. marinum* infections in the non-transplant immunocompetent hosts (12), the majority of transplant patients presented with cutaneous lesions after exposure to the aquatic environment. While multiple lesions may occur, immunocompetent individuals mostly present with a solitary lesion (12). In contrast, all the 6 transplant recipients described in this review had multiple tender erythematous and occasionally ulcerated nodules. These data, albeit anecdotal, suggest that *M. marinum* infections may have a more aggressive course in the immunocompromised transplant population. The skin lesions generally appear in a linear 'sporotrichoid-like' pattern on the exposed extremities. Very rarely does the infection disseminate systemically and this could potentially be due to its optimal growth requirement of lower temperatures between 28°C and 32°C (12). Accordingly, the higher core body temperature may inhibit its systemic dissemination. Nonetheless, sporadic cases of disseminated infections have been observed in

immunocompromised individuals (13–16), as exemplified by the isolation of the organism in the bone marrow (15), blood, and synovial fluid (14). In our review, 1 patient had possible systemic dissemination, as manifested by the presence of skin nodules in both the upper and lower extremities; however, the possibility cannot be ruled out that these lesions could have resulted from simultaneous mycobacterial inoculations at multiple sites.

The diagnosis of *M. marinum* infection should be suspected on clinical grounds in a patient with the typical cutaneous manifestations and who had been exposed to aquatic environment such as fish tanks. This classic clinical presentation is consistent with the waterborne nature of *M. marinum* (13, 15, 17). The diagnosis should be confirmed by histologic and microbiologic methods. In this review, the histologic examination of biopsy specimens showed granulomatous inflammation and fibrosis. A mixture of lymphocytes, macrophages, giant cells, and polymorphonuclear leukocytes may be observed on histopathology (8). A central core of necrosis or abscess was also present in 2 of the cases – a pattern consistent with the typical histologic characteristics of mycobacterial infection (12). Hence, it is important to isolate and identify *M. marinum* in mycobacterial cultures or by genetic probe categorization. Generally, *M. marinum* can be isolated as early as 2–3 weeks after initial incubation, as was observed in our case. It is important to emphasize that *M. marinum* grows best at lower temperatures (28–32°C) so that clinicians need to alert the Mycobacteriology Laboratory if this infection is clinically suspected so that the cultures are incubated at the proper temperature.

M. marinum is susceptible to a host of antibiotics. In a study of 63 cases by Aubry et al. (18), the most common antibiotics used for treatment were clarithromycin, minocycline, doxycycline, rifampin, and ethambutol. In our case, the organism was susceptible to the most commonly used antibiotics for treating this infection, including ethambutol, the rifamycins, and macrolides. Notably, despite the organism's *in vitro* susceptibility to moxifloxacin, our patient did not respond to a 10-day course of empiric moxifloxacin therapy, possibly owing to the very short course of empiric treatment and the need for dual effective therapy for the treatment of *M. marinum* infections (12). Mutational resistance is generally not observed for *M. marinum* infections (18), and hence, the routine use of antimicrobial susceptibility testing has not been recommended (12). However, a case of acquired resistance developing while on rifampin therapy has been reported (14), suggesting the potential need for antimicrobial susceptibility testing if the lesions are not regressing or if the culture remains positive despite 3 months of therapy (12). The *in vitro* susceptibility pattern for *M. marinum* generally parallels clinical response (12). Notably, nearly half of the

patients reported by Aubry et al. received surgical excision or debridement of their lesions (18). In our review, only 1 patient had surgical removal of the nodules because of skin irritation and not because of antibiotic failure.

The exact duration of antibiotic therapy for *M. marinum* infection is not defined in the transplant population, and should be individualized. The recent American Thoracic Society/Infectious Disease Society of America guidelines recommend treating *M. marinum* infection with 2 active antibiotics for 1–2 months after resolution of symptoms, and this generally translates to 3–4 months of total antibiotic therapy (12). Comparatively, the duration of treatment is relatively longer among the 5 previously reported cases, wherein treatment was provided for 3–9 months, with 1 patient developing clinical relapse despite 6 months of ethambutol and ciprofloxacin therapy. In our index case, skin lesions remain at 4 months of treatment, albeit much improved. At the time of this report, our patient had completed 4 months of clarithromycin and rifabutin therapy, and we intend to continue treatment until 2 months following the resolution of his skin lesions.

In conclusion, immunocompromised transplant patients with a history of fish tank exposure, fishing, or swimming should be made aware of the potential risk of *M. marinum* infection. It would be reasonable to advise these individuals to abstain from aquatic activities if they have skin breaks and wounds, and to avoid exposure to aquarium water. Physicians who observe nodular and ulcerated lesions in immunocompromised transplant patients with exposure to marine life should consider *M. marinum* as the potential etiologic agent. High clinical suspicion and early diagnosis are essential to prevent the aggressive nature of this infection in transplant patients. *M. marinum* is generally susceptible to a host of antibiotic agents, but when choosing therapy, one should consider potential drug–drug interaction in this patient population, such as rifampin–cyclosporine interactions (19) or macrolide–cyclosporine interactions (7). The treatment of these infections is also generally more prolonged, possibly as a result of the more extensive clinical disease in the transplant population. With earlier diagnosis and identification of *M. marinum* infections in transplant recipients, potential local spread and systemic dissemination may be prevented.

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