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Exceptional Case

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Cutaneous *Mycobacterium chelonae* infection distal to the arteriovenous fistula

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Abstract

A few single cases of *Mycobacterium chelonae* skin infection have been reported in haemodialysis patients. We report three additional cases that share peculiar clinical characteristics, pointing to diagnostic clues. All three cases presented as erythematous nodules developing distally to a proximal arteriovenous fistula (AVF). This presentation was identical to that of two published cases. A survey of all Belgian haemodialysis units during the period 2007–11 yields an estimated incidence of ~0.9/10 000 patient-years. Although the source of *M. chelonae* remains unclear, this specific clinical presentation should be added to the listing of potential complications of an AVF and should be recognized, as it is fully treatable if diagnosed by culture and tissue biopsy.

Key words: arteriovenous fistula, haemodialysis, *Mycobacterium chelonae*

Background

Over the last 5 years, we diagnosed cutaneous *Mycobacterium chelonae* infection in two haemodialyzed (HD) patients. Both cases presented with erythematous nodules on the arteriovenous fistula (AVF) arm. At diagnosis, the infection had extended to soft tissues and required surgery. We screened all Belgian HD units and identified another case over the same period. On the basis of these three cases and four published single cases [1–4], we conclude that cutaneous *M. chelonae* infection, starting in five cases on the AVF arm, is a rare complication in HD patients. We speculate on the pathogenesis of this complication.

Case reports

All patients were treated by single-use high-flux HD thrice weekly. None was infected with HIV.

Case 1

This patient, a Caucasian woman born in 1945, started HD in 1991 through a left humero-cephalic AVF. She underwent kidney transplantation in 1993 but had to restart HD in May 2008 (in the city of Namur, 60 km south of Brussels) for chronic rejection. Her AVF was still functional. Immunosuppressive drugs were

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stopped; hydrocortisone replacement therapy was initiated for adrenal insufficiency. In August 2009, a skin lesion developed on the third left finger, complicated by osteitis. The two distal phalanges were amputated. One month later, similar lesions developed on the fifth left finger, on the left elbow and on the left thigh. They were red-purple nodular lesions with an abscessed centre. A biopsy showed local granulomatous dermohypodermitis, suggesting mycobacterial infection. The culture grew *M. chelonae*. The isolate showed susceptibility to clarithromycin, linezolid and tobramycin. Clarithromycin and ofloxacin were started in December 2009. Ofloxacin was stopped after 2 weeks because of tendinitis. In September 2010, 2 months after stopping clarithromycin, new lesions appeared on the right thigh and left arm. The lesion on the third left finger started growing again. The biopsy suggested recurrence of mycobacterial infection. Tigecycline and clarithromycin were given for 2 weeks, with clarithromycin continued alone for 12 months. The lesions healed completely, without any relapse as of today.

Case 2

This patient, a Caucasian man born in 1929, was on HD in our unit (Brussels) since June 2010 through a right humero-cephalic AVF. His medical history included type 2 diabetes, ischaemic heart disease treated by coronary artery bypass grafting and chronic atrial fibrillation. In July 2011, a red-purple skin lesion developed on the back of the third metacarpo-phalangeal joint of the right hand (Figure 1). Antibiotics were given without improvement (cefazolin, azithromycin). A biopsy showed lichenified epidermis and a reactive dermal inflammatory infiltrate, rich in neutrophils. A polymerase chain reaction test for atypical mycobacteria was negative. Corticosteroids were injected locally in November 2011, with subsequent further growth of the lesion. Magnetic resonance imaging showed an abscess with infiltration of the tendons. The abscess fistulized to the skin with exposure of the tendons. Light microscopy of aspiration fluid showed the presence of acid-fast bacilli. Rifampicin, ethambutol, pyrazinamide and isoniazid were started. Culture grew *M. chelonae*; the isolate was sensitive to clarithromycin and tobramycin, so treatment was changed to rifampicin, clarithromycin and moxifloxacin. Several surgeries were required. The antibiotics were continued for 10 months, with a slowly favourable evolution. The patient died in July 2013 from an unrelated cause.

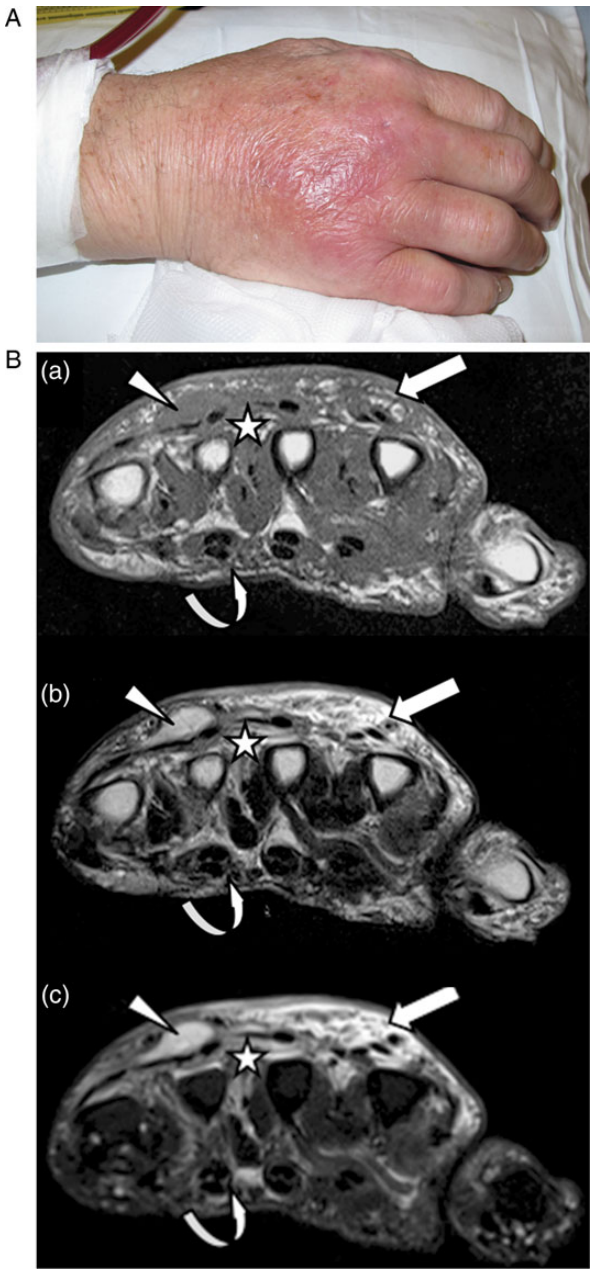

Fig. 1. (**A**) Erythematous, nodular lesion on the back of the right hand, distal to the AVF. (**B**) Transverse (a) T1-, (b) T2- and (c) short tau inversion recovery (STIR)-weighted magnetic resonance imaging. Images at the level of metacarpal bones show severe infiltration of the dorsal soft tissues and extensor tendon sheaths (arrows), with areas of confluence corresponding to abscesses (arrowheads) and extension within the interosseous spaces (star) and volar tendon sheaths (curved arrows).

Screening questionnaire sent to all Belgian HD units

The senior author (M.J.) contacted in 2012 by email the medical directors of all Belgian HD units. The question was: 'Did you have one or more cases of infection by *M. chelonae* in your HD and peritoneal dialysis (PD) patients during the period extending from 1 January 2007 to 31 December 2011?' The response rate to the survey was 98.4%. The survey disclosed an additional very similar case (case 3) in an HD patient and no case in PD patients. As there were 6746 patients on chronic HD in 2009 [5], the middle year of the survey period, the calculated incidence of *M. chelonae* infection is 3 cases/6746 patients/5 years, or 10.9 cases/10 000 patient-years.

Case 3

This patient, a Caucasian man born in 1944, was chronic HD since June 2005 in Mouscron (100 km, west of Brussels) through a left humero-basilic AVF. His past medical history included type 2 diabetes and severe mitral regurgitation. In October 2007, an erythematous, painful skin lesion developed on the third left finger and the finger was swollen. One month later, a biopsy showed a vascular malformation in the deep dermis. Bacteriological analysis showed acid-fast bacilli. Rifampicin and clarithromycin were started. When *M. chelonae* was identified, susceptible to clarithromycin and fluoroquinolones, ciprofloxacin replaced rifampicin and was continued for 3 months together with clarithromycin. The lesion healed and did not relapse.

Table 1. Cutaneous *M. chelonae* infection in HD patients

Reference	Gender	Age, years	Localization of the lesion	Vascular access	Lesion on the AVF arm	Prior IS	Treatment	Relapse
Drouineau *et al.* [2]	F	59	Left hand and forearm	Left humero-basilic AVF	Yes	Yes	Clarithromycin (12 M)	Yes
Abal *et al.* [1]	F	71	Right leg	Unknown	Not applicable	Unknown	Clarithromycin (6 M)	Yes
Kolivras *et al.* [3]	M	70	Left hand and forearm	Left humeral AVF	Yes	Unknown	Clarithromycin (ceftazidime/amikacin)	Patient died
Esteban *et al.* [4]	F	68	Lower limbs	Unknown	Not applicable	Unknown	Erythromycin/amikacin (2 W), then erythromycin alone (4 W)	No
Van Ende *et al.* (this series)	F	64	Left hand	Left humero-cephalic AVF	Yes	Yes	Clarithromycin (6 M) and ofloxacin (2 W)	Yes
	M	82	Right hand	Right humero-cephalic AVF	Yes	No	Rifampicin/clarithromycin/moxifloxacin (10 M) and surgeries	No
	M	63	Left hand	Left humero-basilic AVF	Yes	No	Clarithromycin/ciprofloxacin (3 M)	–

IS, immunosuppressive drugs; M, months; W, weeks.

Discussion

We report three unrelated cases of cutaneous *M. chelonae* infection in HD patients and review four published single cases [1–4]. This rare complication has a peculiar clinical picture. Indeed, nodular lesions developed insidiously on the AVF arm in five of seven cases (Table 1). The other two cases had nodules on one or both legs [1, 4], but their vascular access type was not reported. Why the AVF arm is specifically affected is unclear but striking. Indeed, in Belgium, 30–40% of HD patients have a catheter, but not a single case was observed in patients with a catheter [6]. Overall, this strongly suggests that the AVF plays a role in the pathophysiology of this rare complication.

M. chelonae is one of the most common of the numerous species of rapidly growing non-tuberculous mycobacteria (RGNTM). These ubiquitous organisms survive nutritional deprivation and extreme temperatures and are present in many different environments, including water, soil and dust. They cause respiratory tract infections, skin and soft tissue infections, biomaterial-related infections, osteomyelitis, lymphadenitis and others [7]. Most outbreaks of *M. chelonae* health care–associated infections have been associated epidemiologically with various water sources, including water-based solutions, distilled water, tap water, ice and ice water [7]. In view of the presence, be it at a very low level, of *M. chelonae* in water, and of the recommendation by many HD units to patients to wash the AVF arm with water and soap prior to disinfection and needling for HD sessions [8], it is tempting to speculate that the water used for this washing step may be the source of *M. chelonae*. Indeed, the exit site of an HD catheter is exclusively disinfected with povidone iodine or chlorhexidine and thus is not repeatedly exposed to water, unlike the AVF arm. It should also be mentioned that chlorhexidine-based disinfectants used for disinfection of skin around the AVF and catheter exit site are not bactericidal to *M. chelonae* [7, 9]. Admittedly, the source of *M. chelonae* is only part of the answer, as many other parts of the human body are frequently exposed to water for washing purposes, thus pointing to a potential role for the AVF in this complication.

There are two reports of nosocomial contamination of HD water supplies by RGNTM in HD patients. Twenty-seven cases of RGNTM were observed among 140 HD patients in Louisiana [10]. *M. chelonae* caused 26 of 27 infections. Infections were varied: 14 bacteraemiae, 3 soft tissue infections, 1 access graft infection and 9 disseminated diseases. One factor was common to all patients, they were exposed to reprocessed haemodialysers. The most likely source of infection was the water used to reprocess the dialysers. Indeed, environmental sampling of the water treatment system showed widespread contamination by non-tuberculous mycobacteria. Five cases of systemic *M. chelonae abscessus* infection have also been described in HD patients [11]. *M. chelonae abscessus* was cultured from the hose connected to a water spray device used for manual reprocessing of high-flux dialysers. The germicide used to reprocess dialysers was 2.5% renalin. It did not appear to ensure complete killing of *M. chelonae abscessus* in high-flux dialysers that were manually reprocessed at this HD clinic. In our case series, a nosocomial or common geographic origin is very unlikely because the patients were treated in three different centres in Belgium located 50–100 km from each other. Dialysers were not reused. In addition, the *M. chelonae* isolates showed differences in antibiotic susceptibility. Taken together, these findings strongly suggest that the three isolates were not microbiologically related. The probable cause of the infection was contaminated water exposure in association with AVF disinfection by chlorhexidine, which is unable to kill RGNTM. The other four publications were single cases from different HD units in various countries [1–4].

We can only speculate on the reason(s) why the skin lesions developed distally on the AVF arm. Is it secondary to a circulatory consequence of the AVF, as suggested by Kolivras *et al.* [3]? Are there, distal to the humeral, AVF some local conditions that favour the development of *M. chelonae* (such as low pH, low dissolved oxygen)? That the AVF plays a role in the pathogenesis of this complication is further suggested by the finding that all five cases with infection on the AVF arm were observed in patients with a proximal AVF (i.e. at the humeral level). This is again striking, as, at least in Belgium, proximal AVF accounted for only 25–41% of AVFs during phases 3 and 4 of the Dialysis Outcomes and Practice Patterns Study (Brian Bieber, Arbor Research, Ann Arbor, MI, USA, personal communication). This again suggests a potential role for ischaemia, which is much

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more common with proximal AVFs [12], in the onset of the infection.

Future studies should, whenever possible, obtain molecular patterns of strains (unavailable in our cases), making it easier to exclude (or confirm) nosocomial transmission. In case of nosocomial transmission (very unlikely in our three cases), environmental studies could be helpful. Larger series are also awaited, which should make possible statistical testing of the impact of the proximal AVF location (versus distal).

In conclusion, this is the first case series of cutaneous *M. chelonae* infection in HD patients. All three cases presented with a peculiar clinical presentation. Nodular erythematous skin lesions develop distally to a humeral AVF. Mycobacterial infection should be included in the differential diagnosis of cutaneous nodules in HD patients, especially if they are located distally to a proximal AVF. Biopsies should be performed promptly and analysed by both pathology and microbiology laboratories. This complication is indeed fully treatable if diagnosed.

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Written informed consent was obtained from the subjects as specified in the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Conflict of interest statement

None declared.

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