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REVIEW

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Acid-fast bacteria as causative agents of skin and soft tissue infections: case presentations and literature review

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ABSTRACT

Acid-fast bacteria can be implicated in skin and soft tissue infections. Diagnostic identification can be challenging or not feasible by routine laboratory techniques, especially if there is no access to the Matrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) technology. Here, we present two cases of skin and soft tissue infections caused by two different acid-fast bacteria, *Nocardia brasiliensis* and *Mycobacterium marinum*. They both grew on Löwenstein–Jensen medium, Sabouraud agar medium and blood agar medium. Both bacteria appeared acid-fast by Ziehl–Neelsen stain and Gram-positive by Gram stain. The identification was performed by MALDI-TOF MS and gene analysis. *N. brasiliensis* and nontuberculous mycobacterium *M. marinum* represent rare pathogens that cause severe skin and soft tissue infections. Failure to identify the causative agent and subsequent inappropriate or inadequate treatment may lead to severe complications or even disseminated disease, especially in immunocompromised individuals.

KEYWORDS: *Nocardia brasiliensis*. *Mycobacterium marinum*. Ziehl–Neelsen stain. Acid-fast bacteria. Skin and soft tissue infections. MALDI-TOF MS.

INTRODUCTION

Skin and soft tissue infections (SSTIs) are among the most common infections in outpatient care and the most frequent causes of infection with referrals to emergency departments in the developed world, contributing to significant morbidity and healthcare expenditures. Despite the low mortality associated with SSTIs, the high rates of treatment failure and relapses are of concern. The diagnosis involves clinical history, physical examination, laboratory testing, diagnostic imaging, isolation and identification of the causative agent. Microbiological diagnosis is one of the cornerstones for the management of SSTIs. Prompt procurement and processing of the appropriate samples, evaluation of the laboratory findings (identification of potential pathogens, susceptibility testing) by expert personnel and critical reporting of obtained results support a favorable outcome. In various clinical contexts, the causative agents include Gram-positive cocci, mainly *Staphylococcus aureus* and *Streptococcus pyogenes*, Gram-negative bacteria, *Propionibacterium*, *Corynebacterium*, *Clostridium*, *Pasteurella*, *Nocardia* and *Mycobacterium spp.*

In case acid-fast bacilli are encountered in the clinical microbiology context, more advanced techniques are required in order to identify the causative agent. Two cases of SSTIs caused by two different acid-fast bacteria are presented. Clinical

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presentation, laboratory diagnosis, treatment, as well as difficulties in differentiation and identification of the causative agents are discussed below. A review of published cases during the last 5 years is also presented.

CASE REPORTS

Case 1

A 77-year-old woman, with a medical history of type 2 diabetes mellitus, was referred to the emergency department with painful, exudative and purulent ulceration of the left lower extremity (Figure 1A). The patient recalled a minor trauma two weeks before the presentation and reported sea swimming on a regular basis after the trauma. On admission, routine laboratory work-up revealed elevated WBCs (13,580/mm^3, PMN 84%), C-reactive protein (19.6 mg/dL), and blood glucose (248 mg/dL). Bone X-ray was normal, whereas MRI scanning showed an extended inflammation of the subcutaneous tissue. Debridement of the lesions was performed and the tissue was submitted for microbiological and histological analyses. Both cultures on solid media and histological analyses failed to reveal any infectious agent despite the extended inflammation. However, a blood culture bottle inoculated with the purulent material returned positive after two days of incubation. Gram stain from blood culture smears showed fine and beaded Gram-positive branching bacilli (Figure 2A) and a partially acid-fast

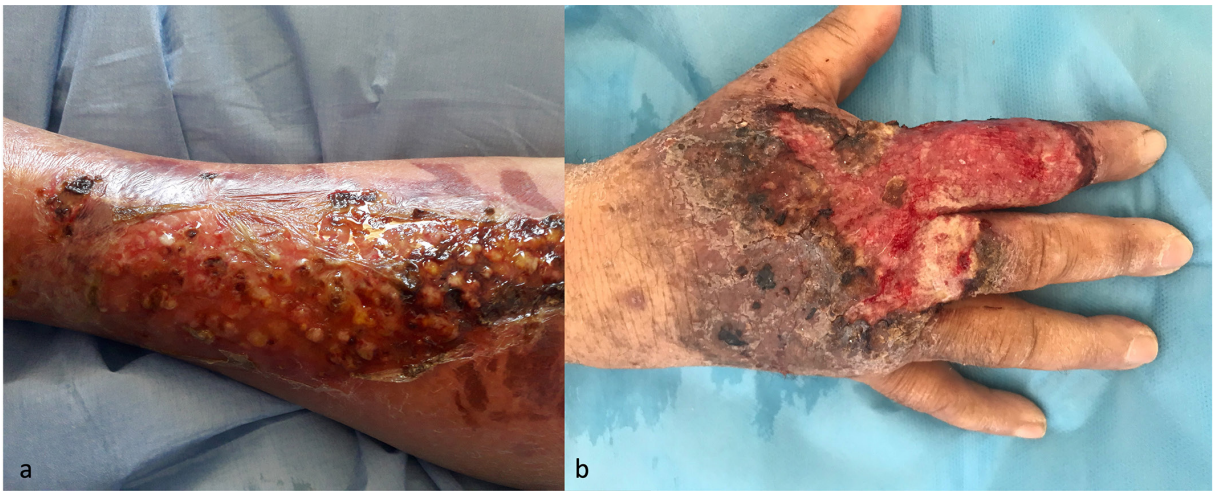

Figure 1 - Clinical presentation: (a) *N. brasiliensis,* (b) *M. marinum.*

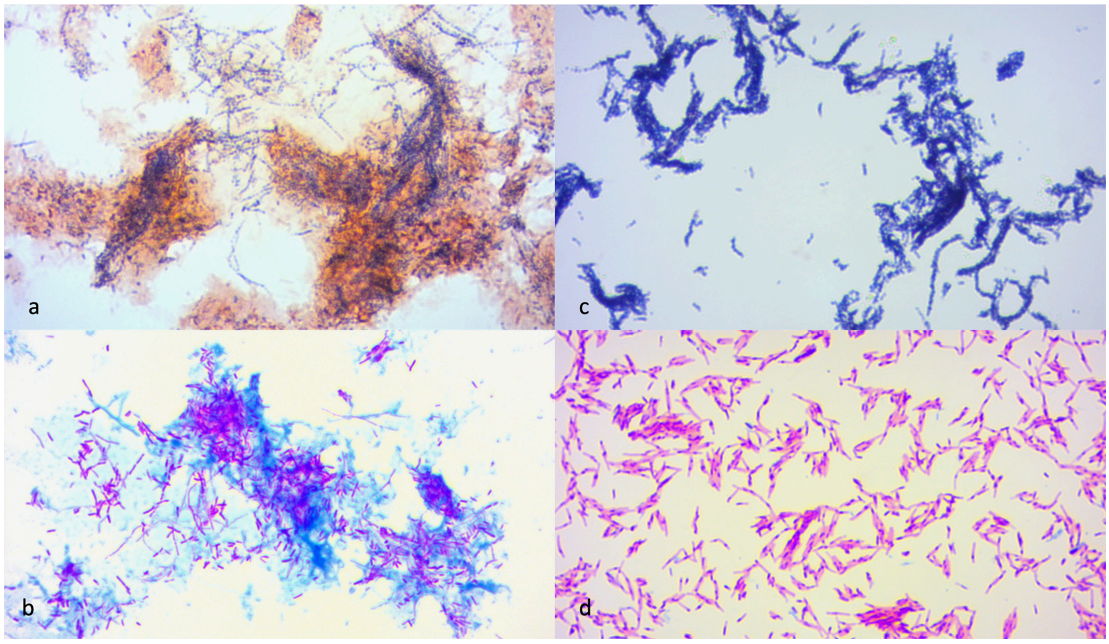

Figure 2 - Gram stain of colonies grown on blood agar (a, c) and Ziehl–Neelsen stain of colonies grown on Löwenstein–Jensen medium (b, d), *N. brasiliensis* (a, b) and *M. marinum* (c, d).

Ziehl–Neelsen (ZN) stain (Figure 2B). Subculture on blood (Figure 3A) and Sabouraud dextrose agar (Figure 3B) plates grew strictly adherent, chalky white colonies, with a moldy odor. In addition, upon completion of 10 days of incubation, growth was observed on Löwenstein–Jensen (LJ) medium (Figure 3C). MALDI-TOF MS analysis identified it at species level as *Nocardia brasiliensis*. MALDI-TOF MS was performed by VITEK® MS system (bioMérieux) by using the knowledge base 3.2 VITEK MS IVD. The identification confidence value was 99.9. The patient was treated with trimethoprim-sulfamethoxazole (TMP-SXT) and discharged with a prescription of a 2-month further course without evidence of relapse.

Case 2

A 63-year-old Caucasian female, with a medical history of ankylosing spondylitis under immunotherapy, was referred to our hospital for having a 3-month history of a rapidly enlarging painful mass with malodorous discharge and surrounding edema on her right hand (Figure 1B). The patient reported that the lesion initially appeared on her right index finger following a minor penetrating trauma by a rose thorn. On admission, the routine laboratory work-up revealed a mild elevation of the erythrocyte sedimentation rate and C-Reactive Protein (45 mm/h and 2.58 mg/dL, respectively). All other tests, including HIV, VDRL and PPD (Mantoux), were either negative or within the normal range. Bone X-rays were normal, whereas an MRI scan revealed an inflammation of soft tissues at the dorsal surface of the hand and a minor lesion at the bone cortex of the lunate bone. Biopsy specimen was submitted for microbiological and histological analysis. Histological analysis failed to identify any infectious agent despite the extended inflammation. Initial cultures on blood and Sabouraud agar plates were negative, however, growth was observed on LJ medium (Figure 3F) after 18 days of incubation. The Gram stain showed short beaded Gram-positive bacilli (Figure 2C), whereas ZN revealed acid-fast bacilli (Figure 2D). Subsequent subcultures were performed on both blood (Figure 3D) and Sabouraud dextrose agar plates (Figure 3E), resulting in the rapid growth of moist, smooth colonies that acquired a yellowish color upon prolonged culture and light exposure. Identification as *M. marinum* was performed by MALDI-TOF MS analysis. MALDI-TOF MS was performed by VITEK® MS system (bioMérieux) using the knowledge base 3.2 VITEK MS IVD. The identification confidence value was 99.9. Results were confirmed by gene analysis using a commercially available DNA strip assay (GenoType Mycobacterium Common Mycobacteria, CM) (HAIN Lifescience, Nehren, Germany).

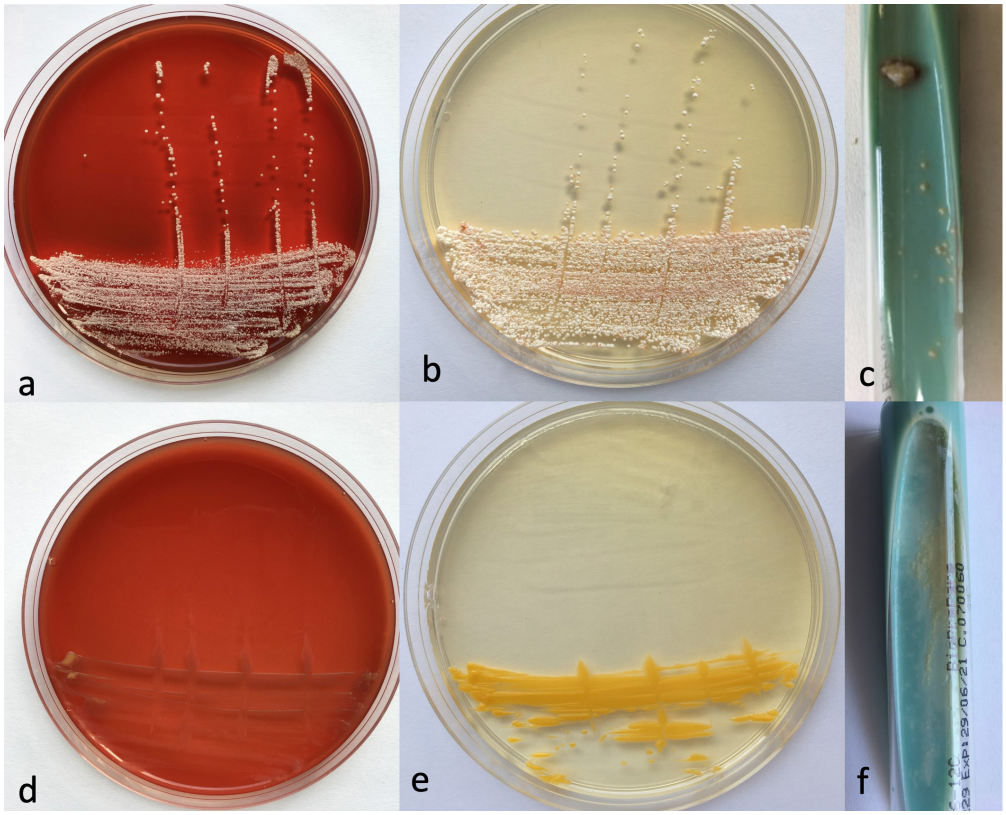

Figure 3 - Colonies of *N. brasiliensis* grown on blood (a), Sabouraud dextrose agar plates (b) and Löwenstein–Jensen medium (c). Colonies of *M. marinum* grown on blood (d), Sabouraud dextrose agar plates (e) and Löwenstein–Jensen medium (f).

The test is based on a PCR technique targeting the 23S rRNA gene region and reverse hybridization of the PCR product to a nitrocellulose strip with immobilized probes for different mycobacterial species. The patient was successfully treated with minocycline and rifampicin and discharged on oral minocycline.

DISCUSSION

We performed a systematic literature review through MEDLINE (U.S. National Library of Medicine) by using the term '*Nocardia brasiliensis*' as well as the term '*Mycobacterium marinum*'. We restricted the search results to reports from 2019 to 2022. All articles written in English referring to skin and soft tissue infections were selected for full-text screening. Cases of disseminated infections and retrospective studies that involved case series published before 2019 were excluded. Regarding *N. brasiliensis,* 14 cases (13 articles) were retrieved, and presented in Table 1[1-13], whereas regarding *M. marinum* 42 cases (39 articles) were retrieved and are shown in Table 2[14-52].

Nocardia and *Mycobacterium spp*. both belong to the family *Mycobacteriaceae* suborder *Corynebacterineae*, order *Actinomycetales*, and, along with other members, such as *Rhodococcus* and *Corynebacteria*, include the most important acid-fast bacteria that may cause disease to humans.

Nocardiosis, although a primarily and increasingly (18-45%) opportunistic infection, affects immunocompetent individuals, some of whom have comorbidities, such as alcoholism and diabetes[53]. About 8-31% of the patients with nocardiosis manifest cutaneous lesions, more commonly in the context of a disseminated disease[54]. On the other hand, primary skin nocardiosis is a rare entity that typically affects individuals without severe immunodeficiencies. It is mainly (80%) caused by *N. brasiliensis*[55]. Clinical presentation can mimic any type of skin and soft tissue infection, such as mycetoma, superficial skin infection (ulceration, abscess, cellulitis) or lymphocutaneous infection with a sporotrichoid pattern[53,54]. Nocardia colonies usually grow in most culture media used for bacteria, fungi or mycobacteria isolation, after 2–5 days of incubation. In some cases, the growth is slow and incubation should be continued for 14-21 days[54]. *Nocardia spp.* typically appear weakly beaded or acid-fast upon traditional ZN staining and acid-fast on modified Kinyoun stain. In the Gram stain, Nocardia appear as Gram-positive beaded branching bacteria[54]. The use of biochemical tests for genus or species identification has been abandoned due to a lack of sensitivity and specificity. The gold standard for the identification of *Nocardia spp.* is molecular biology with amplification and sequencing of one or two gene(s) among rrs, hsp65, secA1 and soda. Nevertheless, MALDI-TOF MS adequately identifies most species in 94-100% of the cases and is increasingly being used[54]. MALDI-TOF MS profiles bacterial proteins from whole cell extracts and obtains a bacterial fingerprint able to identify microorganisms from different genera and species by matching this profile with a reference database. However, caution is required for less common Nocardia species and complexes, such as *N. nova* and *N. abscessus*. In rare species, misidentification is common and the use of molecular biology-based identification remains important in case of a low identification score. Nevertheless, despite its limitations, MALDI-TOF MS is a valuable tool in clinical laboratories enabling rapid identification at least at genus level[53,54].

Diagnosis of nocardiosis may be culture-independent relying only on a PCR-based assay directly on the clinical sample. Advantages include an earlier diagnosis and higher sensitivity, especially in patients already receiving antibiotics. However, just a positive molecular test may only represent colonization and lacks specificity mainly in respiratory samples. Most importantly, antibiotic susceptibility test results are lacking[54]. Regarding the management of primary skin nocardiosis, monotherapy using TMP-SXT is adequate in most cases. Alternative options involve linezolid as initial treatment and minocycline, fluoroquinolones or amoxicillin-clavulanic acid as maintenance treatment[53]. Total treatment duration of 3-6 months is traditionally recommended, although shorter courses may be reasonable in immunocompetent patients[53].

A literature review emphasizes the importance of accurate diagnosis, as in the majority of cases (11/14, 79%), inappropriate medication was administered initially, more commonly cephalosporins. In one case, antitubercular therapy was initially prescribed. Only one (7%) patient was receiving immunosuppressive therapy and two (14%) had diabetes mellitus; therefore, the vast majority were immunocompetent. Injuries have been identified in eight cases (57%), most commonly from gardening and insect bites. The predominant type of infection was the lymphocutaneous-sporotrichoid form (10/14, 71%), whereas primary cutaneous nocardiosis and mycetoma have been described in three cases (21%) and one case (7%), respectively. The lesions were most commonly located on the left hand/arm (9/14, 64%), and, at a lesser extent, on the right hand/arm (4 cases), right leg (1 case) and face (2 cases). All cases had a favorable outcome, most commonly by antimicrobial therapy alone, whereas adjuvant surgical debridement or drainage was required in three cases (21%). TMP-SXT monotherapy was used in eight cases (57%), whereas in

Table 1 - Cases of skin and soft tissue infection caused by *N. brasiliensis* during the last four years (2019–2022).

Article	Gender/Age	Country	Risk factors	Portal of entry	Site	Type of skin lesions	Treatment	Outcome
Lovecchio *et al.*[1]	F/45	Italy		Insect bite	Right leg	Lymphocutaneous form painful/ necrotizing lesion	Linezolid 10d plus TMP-SMX 5 days (disc. cutaneous rash), Amx/CLV p.o. 5 months and linezolid 3 weeks (disc. to anemia)	Cure
Dumic *et al.*[2]	M/66	USA		Injury from gardening	Left hand	Lymphocutaneous form painful/ ulcerated nodular lesion	TMP-SXT plus Amx/CLV 8w	Cure
Acevedo *et al.*[3]	F/50	Switzerland (travel to Greece)		Insect bite	Face, neck	Cutaneous painful/ ulcerated plaque – abscess formation	TMP-SXT disc. drug eruption switched to Amx/CLV 3 months	Cure
Mangieri *et al.*[4]	F/85	Argentina			Left hand	Lymphocutaneous form ulcerated lesion	TMP-SXT 4 weeks	Cure
Chen *et al.*[5]	M/87	China			Left arm	Lymphocutaneous form erythematous papules with purulent secretions	TMP-SXT 4 weeks (Amx/CLV 10d) plus skin lesions debridement/ drainage	Cure
Gil Redondo *et al.*[6]	M/53	Spain	Leflunomide-certolizumab (psoriatic arthritis)		Left wrist	Cutaneous form erythematous-crusted nodule	TMP-SXT 6 months	Cure
Medina-Torres *et al.*[7]	M/12	Mexico		Minor injury due to motor accident	Chest, right axillary and arm	Lymphocutaneous form disseminated nodules	TMP/SXT plus diaminodiphenyl sulfone 6 months	Cure
Wang *et al.*[8]	M/32	China			Left arm	Mycetoma multiple nodules/abscesses	TMP-SXT plus amikacin 6 months	Cure
Li *et al.*[9]	M/34	China			Both arms	Lymphocutaneous form multiple scattered pustules	TMP-SXT 8 weeks (plus linezolid 2 weeks)	Cure
Mu *et al.*[10]	F/42	China		Insect bite	Right hand	Lymphocutaneous form pustule and ulceration	TMP-SXT 6 weeks (14 days amoxicillin)	Cure
Steinmetz *et al.*[11]	M/1.5	USA			Left finger	Cutaneous abscesses	TMP-SXT 7 weeks plus drainage	Cure
Abu Sitta *et al.*[12]	F/57	USA	Diabetes mellitus	Gardening without gloves	Right index finger, forearm	Lymphocutaneous form nodule with swelling and erythema	TMP-SXT 14 days plus drainage	Cure
Al-Obaydi *et al.*[13]	M/75	USA		Arm injury	Left forearm, axilla	Lymphocutaneous form abscess, pain and erythema	TMP-SXT 6 weeks	Cure
Al-Obaydi *et al.*[13]	M/70	USA	Diabetes mellitus	Finger injury while trimming a palm branch	Left ring finger, arm	Lymphocutaneous form draining abscess, cellulitis, lymphadenitis	TMP-SXT 6 weeks	Cure

TMP-SMX = trimethoprim-sulfamethoxazole; Amx/CLV = amoxicillin/clavulanic; disc. = discontinued due to

Table 2 - Published cases of skin and soft tissue infection caused by *Mycobacterium marinum* during the last four years (2019–2022).

Article	Gender/ Age	Country	Medical history	Portal of entry/ source of exposure	Site of infection	Type of skin lesions	Treatment	Outcome
Khadka *et al.*[14]	F/45	Nepal	Corticosteroids, methotrexate, hydroxychloroquine	Fish handler	Left hand, forearm and arm	Lymphocutaneous form erythematous painful nodules with discharge, swelling of the left hand	Ethambutol plus Clarithromycin plus Doxycycline 8 months	Cure
Cascardo *et al.*[15]	F/41	USA	Infliximab, methotrexate, prednisone (inflammatory polyarthropathy, Crohn's disease)		Upper back	Pruritic, tender erythematous papules and pustules	Clarithromycin plus Ethambutol – ND	ND
Li *et al.*[16]	F/35	China		Lobster pinch	Right index finger	Progressive swelling, pus drainage	Rifampicin plus Clarithromycin 3m plus surgical drainage	Cure
Iwata *et al.*[17]	F/63	Japan			Submandibular	Submandibular nodule	Clarithromycin plus Ethambutol 4 weeks	Cure
Liu *et al.*[18]	F/68	China		Wound on left middle finger, cleaning fish from local market	Both hands	Painless plaques	Doxycycline plus Clarithromycin 5 months	Cure
Riccardi *et al.*[19]	M/51	Italy	Adalimumab (psoriasis)	Octopus fisherman, skin puncture while fishing	Left hand and wrist	Reddened ulcerated lesion	Clarithromycin, plus Rifampicin plus Ethambutol 6–9 months	Cure
Seidel *et al.*[20]	M/36	Brazil		Fishing, trauma with a perforating-cutting tool	Left hand, especially the fifth finger	Papule and exudation, progression to an erythematous-verrucous plaque with nodules and crusts, evident atrophy of the fifth finger	Clarithromycin plus Doxycycline plus Rifampicin	Cure
Patel *et al.*[21]	M/61	USA	Adalimumab (psoriatic arthritis)		Right forearm	Small blister-like lesion which upon removal/ resection became ulcerative	Azithromycin (disc. diarrhea) plus Rifampin, then Ethambutol plus Rifampin (disc. resistance), then Ethambutol plus Rifabutin 5 months	Cure
Xing *et al.*[22]	M/38	China		Owner of a seafood market, fish bite	Right middle finger, right hand and elbow	Lymphocutaneous form poorly healed primary wound on the right middle finger, secondary ulcerated mass on right hand, subcutaneous nodule at the right elbow and supratrochlear lymph nodes	Rifampin plus Minocycline plus Clarithromycin 9 months	Cure
Vanhooteghem *et al.*[23]	M/41	Belgium		Fish manicure-Thailand vacation	Left thumb	Hardened, rough, brownish erythematous periungual plaque	Doxycycline 4 months	Cure
Trčko *et al.*[24]	M/37	Slovenia		Aquarium owner (tropical fish, exotic snakes, lizards)	Right hand	Small warty papule progressed to erythematous scaling plaque on the fourth finger, after a few months a new lesion appeared on the back of his hand and the extensor side of the right wrist.	Rifampicin plus Clarithromycin 6 months	Cure
Wenlong *et al.*[25]	M/18	China		Chef	Left hand	Plaques and nodules	Photodynamic therapy combined with fractional CO_2 laser ablation	Cure
Wenlong *et al.*[25]	F/70	China		Stabbed by a fish	Right arm	Painful ulcer on her right forearm	Photodynamic therapy combined with fractional CO_2 laser ablation	Cure

Table 2 - Published cases of skin and soft tissue infection caused by *Mycobacterium marinum* during the last four years (2019–2022) (cont.).

Article	Gender/ Age	Country	Medical history	Portal of entry/ source of exposure	Site of infection	Type of skin lesions	Treatment	Outcome
Patel *et al.*[26]	F/61	USA	Sjögren's syndrome, chronic left upper extremity edema (breast cancer – mastectomy, lymphadenectomy, chemotherapy)	Knife injury to her left thumb while cutting fish	Left arm	Lymphocutaneous form pustule at the primary site, additional nodular lesions ascended up her arm to the level of her elbow with associated erythema and drainage	Clarithromycin plus Ethambutol plus Rifampin. Plan for surgical debridement (due to slow improvement at follow-up)	Slow improvement
Su *et al.*[27]	F/63	China		Cut injuries on her hands while cleaning fish	Both arms	Painful pink nodules and ulcerations with hemorrhagic crust on both arms	Moxifloxacin plus Rifampin plus Clarithromycin 6 months	Cure
Rathish *et al.*[28]	F/30	India		Cut injury to the right wrist while cleaning a fishbowl	Right forearm	Lymphocutaneous form multiple nodules with a large nodule that had formed an abscess	Rifampicin plus Clarithromycin – ND	Cure
Costescu Strachinaru *et al.*[29]	F/60	Belgium		Owner of a tropical fish tank. Injured by a plant thorn while gardening	Right arm	Lymphocutaneous form nodular lesions	Clarithromycin 14 months	Cure
Rida *et al.*[30]	F/53	Lebanon	Golimumab	Exposure to fresh fish	Right hand	Non-resolving indurated plaque over the base of the right fifth digit right hand	Clarithromycin plus Doxycycline – ND	Cure
Tuan *et al.*[31]	M/46	USA		Fishing expedition, finger injury and wound exposure to shellfish	Left hand	Hyperkeratotic plaques without erythema	Rifampin plus Clarithromycin plus Ethambutol 4 months	Cure
Briand *et al.*[32]	M/7	France		Played in a pond a few weeks before the abscesses	Both hands and right arm	Lymphocutaneous form multiple inflammatory cutaneous lesions on both hands and suppurative adenopathy of the right arm	Clarithromycin 1 month	Cure
Bezerra *et al.*[33]	M/52	Brazil		Bathing in ponds, fishing activities and handling fish, trauma caused by a cactus thorn	Right lower limb	Chronic and extensive cutaneous infection Dyschromic atrophic center plate and verrucous borders with hematic crusts	Ethambutol plus Rifampicin plus TMP-SXT 6 months leaving a dystrophic atrophic plaque	Cure
Furuichi *et al.*[34]	M/49	Japan	Infliximab (psoriatic arthritis)	Caring for tropical fish	Right arm	Lymphocutaneous form indurated erythema appeared on the dorsal surface of the third digit of the right hand, followed by painful subcutaneous nodules that spread along the lymphatic vessels on the right arm	Infliximab infusion was discontinued. Moxifloxacin plus Doxycycline plus TMP-SXT 4 months. Infliximab was restarted due to arthritis recurrence within the last 3 months	Cure
Furuichi *et al.*[34]	M/58	Japan	Adalimumab, methotrexate (psoriatic arthritis)	Caring for tropical fish	Right arm	Lymphocutaneous form erosive erythema on the dorsal surface of the third digit of the right hand and subcutaneous nodules along the lymphatic vessels of the right arm	Adalimumab was discontinued. Clarithromycin plus Ethambutol plus Doxycycline 5 months, Brodalumab was administered because of arthritis recurrence	Cure
Zimmerlich *et al.*[35]	M/48	Germany	Infliximab (ulcerative colitis)	Small wound on his right ring finger – cleaning his two aquariums without gloves	Right arm	Lymphocutaneous form, lesion on the nailfold of the right ring finger and multiple painless skin lesions on his right upper extremity	Clarithromycin plus Ethambutol plus Rifampicin 12 months plus Percutaneous abscess drainage. Then Clarithromycin plus Rifampicin 14 months	Cure

Table 2 - Published cases of skin and soft tissue infection caused by *Mycobacterium marinum* during the last four years (2019–2022) (cont.).

Article	Gender/ Age	Country	Medical history	Portal of entry/ source of exposure	Site of infection	Type of skin lesions	Treatment	Outcome
Nachimuthu *et al.*[36]	F/53	USA	Golimumab (rheumatoid arthritis), diabetes	Cleaning her fish tank with bare hands, use of lancets for checking blood glucose, injuries from rose thorns	Left arm	Lymphocutaneous form tender nodules with surrounding redness on her left index finger and forearm.	Minocycline plus Clarithromycin 9 months	Cure
Berman *et al.*[37]	M/70	USA	Golimumab (ulcerative colitis)	Cleaning his fish tank	Left hand, arm	Lymphocutaneous form, single erythematous indurated plaque with a central ulcer on his left hand and painful nodules on his left arm	Minocycline 1 week, then Rifampin plus Minocycline (given his immunomodulatory state) 10 weeks	Cure
Bachiyska *et al.*[38]	F/66	Bulgaria		Hand injury, cleaning an ornamental tropical fish aquarium without using protective gloves.	Right arm	Lymphocutaneous form small red-violet papules on right hand and forearm, some progressed to pustules and ulcers, in straight line proximally	Rifampicin plus Ethambutol, after 2 months disc. joint pain, candidiasis, diarrhea, intestinal pain – continued with symptomatic therapy, lesions slowly improved after 8 months	Cure
Bachiyska *et al.*[38]	M/50	Bulgaria		Fisher and diver, stab wound on the right hand little finger by a fish fin	Right hand	Lesions on the little finger and the thumb, progression to deep tissue infection of wrist	Rifampicin plus Ethambutol for 1 month, plus Clarithromycin for the next 6 months	Cure
Peña Merino *et al.*[39]	F/54	Spain	Adalimumab (rheumatoid arthritis)	Cut on the finger while preparing fish in her workplace.	Left hand	Multiple erythematous-violaceous papules on the left hand and wrist	Minocycline 2 months; despite marked improvement, some active lesions persisted; treatment was switched to Clarithromycin	Cure
Park *et al.*[40]	F/74	Korea	Local steroid injection in the elbow to treat arthritis	Trimming oysters	Left arm, trunk	Diffuse tender erythematous and yellow cellulitis-like patches on her left arm, discrete papules on the left trunk	Doxycycline plus Clarithromycin plus Rifampin 3 months, moderate improvement – lost to follow-up	Moderate improvement –lost to follow-up.
Bollam *et al.*[41]	M/33	USA		Landscape work, in which he might have a skin injury, owner of fish tank (without fish)	Right hand	Nodular skin lesion on the right index finger	Incision and drainage of the nodule with excision of a deep mass, advised to follow-up outpatient for further care	ND
Chokevittaya *et al.*[42]	M/53	Thailand		Ant bite while gardening near a pond, hobbies: gardening, decorating corals at his home.	Left hand	Progressive swelling of his left index finger for 4 months, abscess formation	Rifampin plus Clarithromycin plus Streptomycin plus multiple surgical debridements	Cure
Drakou *et al.*[43]	M/48	Greece	Infliximab (ankylosing spondylitis), oral steroid treatment	Puncture on his left index finger while working at an underwater ship repair	Left hand and forearm	Lymphocutaneous form painful swelling over the affected area, subcutaneous abscesses	Anti-TNFa was discontinued, surgical intervention, Clarithromycin plus Ethambutol plus Rifampicin	Cure
Conforti *et al.*[44]	M/66	Italy		Aquarium owner	Left hand	Two purplish painful nodules on the left hand	Clarithromycin 4 weeks	Cure
Assiri *et al.*[45]	M/72	France	Cyclosporin, steroids, mycophenolic acid (kidney transplant patient)	Minor trauma (cut) while cleaning his fish tank	Right hand	Asymptomatic, erythematous, scaly nodule over the proximal interphalangeal joint of the right index finger	Immunosuppressive treatment was reduced (cyclosporin dosage was lowered), Minocycline 2 months, switched to Doxycycline 3 months	Cure

Table 2 - Published cases of skin and soft tissue infection caused by *Mycobacterium marinum* during the last four years (2019–2022) (cont.).

Article	Gender/ Age	Country	Medical history	Portal of entry/ source of exposure	Site of infection	Type of skin lesions	Treatment	Outcome
Feng *et al.*[46]	M/53	China		Scratch on the nose root by a rusty shrimp cage	Face, neck	Lymphocutaneous form erythematous papules and plaques on the nose root, abscesses on the neck and face, cervicofacial lymphadenitis	Rifampin plus Ethambutol plus Minocycline 3 months	Cure
Vemulakonda *et al.*[47]	M/69	USA		Cleaning an aquarium at home	Right arm	Lymphocutaneous form verrucous plaques on the right elbow and ulcerated papulonodules on the right arm	Rifampin plus Ethambutol, ongoing therapy	Considerable improvement
Esteves *et al.*[48]	M/65	Portugal		Gardening-rose thorn injury to the left thumb. Cleaning an aquarium.	Left hand and forearm	Lymphocutaneous form erythematous nodules in a linear distribution along the left hand and forearm.	Clarithromycin plus Rifampicin 6 months	Cure
Bouceiro-Mendes *et al.*[49]	M/33	Portugal		Minor cut on the finger, cleaning an aquarium of tropical fish without hand protection.	Right hand and forearm	Lymphocutaneous form ulcerated nodule on the right fingertip, painful plaques and nodules, some suppurative, on the right hand and forearm	Clarithromycin plus Ethambutol plus Rifampicin 9 months	Cure
Kobayashi *et al.*[50]	M/73	USA	Prednisone (Crohn's Disease)	Salt and fresh water fish tank that he routinely cleaned and maintained	Hands, face and trunk	Several erythematous nodular lesions on bilateral hands and erythematous papules on his chest, abdomen, face and extremities	TMP-SXT (*Nocardia* was suspected – rash improved) plus Rifabutin, ongoing therapy	Improvement
Koushk-Jalali *et al.*[51]	M/66	Germany	Myelodysplastic syndrome (treated with subcutaneous erythropoietin injections)	Aquarium hobbyist	Right hand and arm	Lymphocutaneous form, nodules and plaques that firstly occurred on the right index finger and spread to the fore- and upper arm along the lymphatic vessels	Rifampicin plus Ethambutol was initiated, with almost complete clearance of the skin lesions within 8 weeks, ongoing therapy	Cure
Sahuquillo-Torralba *et al.*[52]	M/10	Spain		Skin abrasion, bathing with a tortoise, swimming in pools	Right knee	Erythematous plaque	Clarithromycin 5 months	Cure

ND = no data provided; disc. = discontinued due to, TMP-SXT = trimethoprim-sulfamethoxazole.

six cases, the latter was combined with other regimens, namely amoxicillin/clavulanic, linezolid, amoxicillin and amikacin. TMP-SXT was discontinued in two cases due to cutaneous reactions.

Regarding mycobacterial cutaneous infections, including cutaneous manifestations of *Mycobacterium tuberculosis* infection, leprosy caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, and infections caused by nontuberculous mycobacteria (NTM), they exhibit widely different clinical presentations, such as cellulitis, non-healing ulcers, subacute or chronic nodular lesions, abscesses, superficial lymphadenitis and verrucous lesions[56]. More specifically, NTM involve slowly growing *M. ulcerans*, *M. marinum*, *M. kansasii*, *Mycobacterium avium-intracellulare* complex and *M. haemophilum* and the rapidly growing mycobacteria: *M. fortuitum*, *M. abscessus* and *M. chelonae*. Although most NTM are opportunistic pathogens, *M. marinum*, as well as its related species, *M. ulcerans*, are pathogenic mycobacteria, and can cause disease in healthy individuals[56].

The two main predisposing factors for *M. marinum* infection are exposure to *M. marinum*-infected freshwater or saltwater, and the presence of superficial cuts or abrasions[57]. Thus, the aquarium or fishery workers and fish hobbyists are at risk, especially if they do not use waterproof gloves for protection.

Cutaneous manifestations vary but mainly include a solitary papule or nodule that may ulcerate and spread in a sporotrichoid pattern (lymphangitic spread). *M. marinum* may produce deep tissue involvement or disseminated disease, especially in immunocompromised hosts[57]. Because its optimal temperature for growth is around 30°C, cutaneous lesions most frequently occur in the upper or lower extremities[56,57].

M. marinum grows slowly and positive cultures may be obtained after 3-4 weeks, whereas in subculture, the growth

rate can be slower between 4 to 14 days[57]. *M. marinum* is less demanding than *M. tuberculosis* and growth can be observed even on conventional media such as blood agar[57]. In our settings, *M. marinum* fluently grew on blood and even on Sabouraud dextrose agar (peptone, glucose and agar). This is the first report – to the best of our knowledge – of the abundant growth of *M. marinum* on Sabouraud agar medium. Phenotypically, colonies of *M. marinum* are white or beige when the media are kept in the dark, but yellowish-orange after exposure to light (photochromogenicity)[57]. According to recently proposed guidelines, all clinically relevant isolates of NTM should be identified by molecular methods[58]. PCR-based commercial methods developed for the identification of *M. marinum* include INNO-LIPA Mycobacteria v2 (Innogenetics), based on the amplification of the ribosomal gene spacer (16S-23S), and Genotype Mycobacteria CM/AS (Hain Lifescience), based on the amplification of a 23S rRNA gene[57]. The drawback is that they cannot differentiate *M. marinum* from *M. ulcerans*, as their rRNA sequences are similar[57]. On the other hand, the discriminatory power of MALDI-TOF MS method regarding NTM has increased with recent improvements of protein extraction protocols and databases but not all species and subspecies can be differentiated with this approach[58]. MALDI-TOF MS has achieved up to 98% agreement with 16S rRNA, hsp65 and rpoB genes sequencing[59]. Ancillary to physical examination and medical history, a positive result of an interferon-gamma release assay for tuberculosis may provide an important diagnostic clue, before the laboratory confirmation is provided[36].

There is no consensus on the optimal treatment of *M. marinum* infection. Antimicrobials used include clarithromycin, ethambutol, rifampin, minocycline, doxycycline and trimethoprim-sulfamethoxazole. Monotherapy has been proven successful in most cases, especially for superficial cutaneous infections[57]. Treatment is continued 1-2 months after the resolution of skin lesions, typically 3-4 months in total[50]. Combination therapy is preferred in deeper infections. Excellent outcomes have been reported for the combination of clarithromycin-rifampicin, as well as the combination of ethambutol-rifampicin. Nevertheless, the combination of clarithromycin and ethambutol seems to provide the optimal balance of efficacy and tolerability for most patients, with the addition of rifampicin in cases of osteomyelitis or other deep structure infection[58]. The latter approach is recommended by the Infectious Diseases Society of America and American Thoracic Society[31]. Surgical debridement may be required for patients with deeper or more complicated infections, or in cases of poor response to treatment[57]. Thermotherapy and photodynamic therapy combined with fractional CO_2 laser ablation have been reported as effective alternatives. Furthermore, consideration should be taken to limit immunosuppression in patients with *M. marinum* infection by discontinuing their treatment, particularly when receiving TNF-alpha inhibitors[31].

The literature review reveals that in half of the cases (18/42, 43%) inappropriate medication was administered initially, more commonly cephalosporins, TMP-SXT, fluoroquinolones, as well as antifungals. In four cases, steroids were prescribed as the lesions were considered to have an allergic or autoimmune basis. Fourteen patients (33%) were receiving immunosuppressive therapy and the vast majority of them (12 patients) were under anti-TNFa regimens. In addition, another patient had Sjögren's syndrome without receiving therapy, one had myelodysplastic syndrome and one was receiving steroid injections. Injuries have been identified in 25 cases (60%). Although in some cases patients do not recall a trauma, their habits or occupations (chef, fishermen, landscape enthusiasts) may predispose them to minor injuries. Source of exposure is speculated in almost all cases (39/42, 93%); specific direct exposure to fish occurred in 35 cases (83%), exposure to fresh or salt water (pool, pond, sea) in 3 cases (7%) and possible occupational exposure in one case (chef). The infection was presented as lymphocutaneous-sporotrichoid form in 43% (18/42) of the cases and the lesions were most commonly located on the upper extremities (37/42, 88%), specifically right hand/arm (18 cases, 43%), left hand/arm (15 cases, 36%), both arms (4 cases, 10%) and, at a lesser extent, on the right leg, face, neck and trunk. With the exception of two cases that exhibited slow or moderate improvement and two that did not include information regarding the follow up, all other cases had a favorable outcome, most commonly by antimicrobial therapy alone, whereas adjuvant surgical intervention was required in six cases (14%). In addition, the immunosuppressive therapy was discontinued in four cases (three cases considered patients receiving anti-TNFa). The most commonly used regimen combinations were clarithromycin plus rifampicin plus ethambutol (seven cases), clarithromycin plus rifampicin (five cases), and ethambutol and rifampicin (three cases). Clarithromycin and minocycline were used as monotherapy in five and three cases, respectively.

In this article, we have chosen to co-present these two pathogens as they share common properties. Both represent 'rare' causes of skin and soft tissue infections. Diagnosis is challenging as the clinical presentation overlaps with other more common pathogens. On the other hand, lymphocutaneous infection with the characteristic sporotrichoid pattern can drive diagnosis to both pathogens

or sporotrichosis (caused by *Sporothrix schenckii*), almost obsolete in Europe. Both pathogens cause infections that are not transmissible between humans and are usually acquired from natural sources, like soil and water, through skin abrasions. Although other species of their genera typically affect immunocompromised individuals, *N. brasiliensis* and *M. marinum* can cause disease in immunocompetent persons. Nevertheless, we should keep in mind that although they mainly affect immunocompetent individuals, both diseases could be detrimental for immunocompromised patients and may lead to disseminated disease. Moreover, there are several difficulties in their isolation, as direct microscopy and cultures are often negative due to low bacterial load, inappropriate sampling – biopsies are preferable to swabs but more difficult to obtain –, improper laboratory handling, need for prolonged incubation, selective growth media and additional incubation at 30 ºC. In many cases, repeated sampling or biopsies are required in order to achieve the diagnosis. Nevertheless, although 'uncommon', these pathogens should be included in the differential diagnosis as they are encountered, especially in secondary and tertiary health care units. Most patients have undergone inappropriate treatment and seek advice in health care facilities providing specialist services, such as dermatologists, infectious disease physicians and clinical microbiologists, as well as specialized laboratory facilities.

A comparative presentation of *N. brasiliensis* and *M. marinum* colonies on culture media highlights their common features. Both bacteria can be isolated on media suitable for mycobacteria, such as LJ, as well as on common media, such as blood agar and Sabouraud dextrose agar plates. In addition, both isolates could be stained similarly by both Gram stain and ZN stain. *N. brasiliensis* isolate retained the characteristic beaded pattern on Gram stain and was easily stained by ZN, almost evenly, in both conventional and modified staining methods. In terms of *M. marinum*, it was readily stained by ZN, as expected, but it was also stained by Gram stain as Gram-positive; this finding, along with the ability to grow on conventional media, was challenging or even misleading to the species identification. Similarity in microbiological and clinical manifestation of nocardiosis and mycobacterial infections, resulting in the difficulty of accurate identification, has been already described in respiratory samples[60]. The literature review revealed that, in a nocardiosis case, the patient was treated for mycobacterial infection based on clinical appearance of the lesions and local epidemiology[8], whereas one patient with *M. marinum* cutaneous infection was treated for *Nocardia spp.* infection based on Gram and ZN stain of biopsy specimens[50].

CONCLUSION

To conclude, skin and soft tissue infections can pose diagnostic dilemmas in the case that 'uncommon' pathogens are encountered. This can lead to misdiagnosis and unappropriated or delayed treatment. Therefore, close collaboration among physicians and clinical microbiologists, expertise of scientific personnel and application of current techniques, molecular and MALDI-TOF MS are essential prerequisites for a precise diagnosis. The laboratory should be informed if *Nocardia* or *Mycobacterium spp*. are included in the differential diagnosis. Proper processing of samples, including inoculation on suitable culture media and growth conditions, is vital to optimize the laboratory diagnosis. Laboratory results influence therapeutic decisions and may have a substantial impact on patient care and outcome.

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