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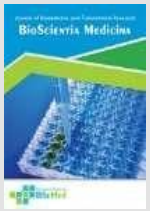

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Mycobacterium marinum Co-infection Masquerading as Treatment-Resistant Chromoblastomycosis: A Diagnostic and Therapeutic Challenge in Cutaneous Co-infection

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A B S T R A C T

Background: Co-infection of chromoblastomycosis and *Mycobacterium marinum* (fish tank granuloma) within a single cutaneous lesion is exceptionally rare and presents a formidable diagnostic challenge owing to overlapping clinical and histopathologic features. The chronic verrucous or nodular morphology, predilection for distal extremities, and aquatic exposure history common to both conditions can lead to misdiagnosis, prolonged ineffective therapy, and patient morbidity. **Case presentation:** A 31-year-old Indonesian male with a fishkeeping hobby presented with a persistent erythematous plaque on the right middle finger, present since 2022, following a puncture injury sustained while collecting mosquito larvae and water fleas as fish food. He was initially diagnosed with chromoblastomycosis (*Phialophora* spp. on culture) in September 2023 and treated with itraconazole 200 mg daily and topical miconazole 2% for 48 weeks without resolution. Repeat biopsy in 2024 demonstrated negative periodic acid-Schiff and Ziehl-Neelsen stains but revealed non-caseating tuberculoid granulomas. Considering the patient's aquatic exposure, antifungal failure, and granulomatous histopathology, a diagnosis of fish tank granuloma due to *M. marinum* co-infection was established. Combination antimycobacterial therapy with rifampicin 600 mg and ethambutol 1500 mg daily produced clinical resolution at six-month follow-up. **Conclusion:** This case underscores the necessity of considering M. marinum in patients with antifungal-refractory chronic skin lesions and aquatic exposure, and highlights the diagnostic value of repeat histopathology with directed staining when initial therapy fails.

1. Introduction

Mycobacterium marinum is an atypical, slow-growing nontuberculous mycobacterium found ubiquitously in fresh and saltwater environments worldwide, including aquariums, swimming pools, fish ponds, and natural bodies of water.[1,2] Cutaneous infection by *M. marinum* — colloquially termed fish tank granuloma or swimming pool granuloma — typically arises through traumatic inoculation of the organism from contaminated water or aquatic organisms into superficial skin trauma, with predilection for the distal extremities, particularly the dorsum of the hand and fingers.[3,4] Reported incidence is approximately 0.04 to 0.27 cases per 100,000 person-years in the general population, but is substantially elevated among aquaculture workers,

ornamental fish enthusiasts, and individuals engaged in marine occupations.[2,5]

Chromoblastomycosis is a chronic, deep-seated cutaneous and subcutaneous mycosis caused by pigmented (dematiaceous) saprophytic fungi, principally species within the genera *Fonsecaea*, *Phialophora*, *Cladophialophora*, and *Rhinocladiella*.[6,7] The disease is endemic to tropical and subtropical regions, predominantly affecting agricultural and forest workers exposed to soil, decaying vegetation, or organic plant matter through traumatic inoculation. Clinically, chromoblastomycosis manifests as slowly progressive nodular, verrucous, plaque-like, or tumorous lesions, most often on exposed lower extremities, with a histopathologic hallmark of brown-pigmented sclerotic bodies (medlar bodies, copper pennies) within mixed inflammatory infiltrates.[6,8]

Both *M. marinum* infection and chromoblastomycosis can present clinically as chronic, indurated, verrucous or nodular lesions with delayed presentation and significant morphologic overlap, generating substantial diagnostic confusion.[9,10] Histopathologic distinction is similarly challenging when classical sclerotic bodies of chromoblastomycosis are sparse or absent, and when *M. marinum* produces non-caseating tuberculoid granulomas indistinguishable from those of cutaneous tuberculosis or sarcoidosis.[11,12] Furthermore, the diagnostic yield of conventional staining methods is limited: Ziehl-Neelsen stains for *M. marinum* achieve positivity rates of only 30%, and culture identification, while more sensitive (70-80%), requires 2 to 6 weeks under specialized conditions.[1,4]

True co-infection of *M. marinum* and chromoblastomycosis within a single anatomic lesion is exceedingly uncommon, with only sporadic reports in the international literature.[9,13] Such co-infection is thought to require concurrent traumatic inoculation of both pathogens or sequential opportunistic infection in compromised tissue. The clinical relevance of recognizing this entity lies in the divergent therapeutic implications: chromoblastomycosis demands prolonged systemic antifungal therapy (typically itraconazole or terbinafine), whereas *M. marinum* requires combination antimycobacterial therapy (rifampicin plus ethambutol or clarithromycin).[1,14] Misdirected single-pathogen therapy may permit unrecognized co-pathogen progression, resulting in treatment failure and prolonged morbidity, as exemplified by the present case.

We report a rare case of *M. marinum* and chromoblastomycosis (*Phialophora* spp.) co-infection in a 31-year-old fishkeeper that initially manifested as antifungal-refractory chromoblastomycosis and was ultimately diagnosed through repeat histopathology demonstrating non-caseating granulomas in conjunction with relevant aquatic exposure history. The novelty of this report lies in its longitudinal documentation over 30 months, the detailed comparative histopathologic analysis between initial and follow-up biopsies, and the dramatic clinical response to antimycobacterial monotherapy, which collectively support the existence of true cutaneous *M. marinum*–chromoblastomycosis co-infection as a clinical entity warranting heightened diagnostic vigilance among dermatologists, particularly in tropical regions with extensive aquaculture and fishkeeping populations. The serial clinical evolution of the lesion is shown in Figure 1, the histopathologic features supporting the revised diagnosis are illustrated in Figure 2, and the integrated diagnostic and therapeutic milestones over the 30-month period are summarized in Figure 3.

2. Case Presentation

Patient demographics and clinical presentation

A 31-year-old Indonesian male was referred to the Dermatology and Venereology outpatient clinic at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Indonesia, with a chief complaint of a persistent reddish nodule on the right middle finger that had been present for over two years without satisfactory clinical response to prolonged antifungal therapy. The patient denied any history of diabetes mellitus, hypertension, autoimmune disease, drug allergies, or

food allergies. He was otherwise systemically healthy and was a non-smoker with no significant travel history outside Indonesia. The patient's demographic profile, occupational and recreational exposure history, and key clinical characteristics at the time of initial presentation are detailed in Table 1.

Table 1. Demographic, clinical, and exposure characteristics of the patient at presentation.

Characteristic	Finding
Age, gender	31 years, male
Nationality/region	Indonesian; resident of Bali, Indonesia
Occupation/hobby	Office worker; ornamental fishkeeping hobbyist
Aquatic exposure	Daily handling of aquarium water; collected mosquito larvae and water fleas as fish food
Trauma history	Puncture injury to the right middle finger in 2022 while collecting larvae
Comorbidities	None (no DM, HTN, autoimmune disease, allergies)
Lesion site	Digiti III manus dextra (right middle finger), dorsal aspect
Lesion morphology	Solitary erythematous plaque, well-defined border, geographic shape, 1.5 × 2 cm
Lesion duration at presentation	≈ 30 months (since 2022)
Mucous membranes/hair/nails	Unremarkable
Sweat gland function	Normal
Lymphadenopathy	Absent
Sensory examination	Intact; no nerve thickening

DM = diabetes mellitus; HTN = hypertension. *Aquatic exposure considered the most probable inoculation route for both pathogens.

History of presenting illness and aquatic inoculation

The lesion first appeared in 2022 after the patient sustained a puncture injury to the right middle finger while collecting mosquito larvae and water fleas to feed his ornamental aquarium fish. The injury was minor, did not bleed substantially, and was not formally cleaned or treated. The patient continued his aquatic activities without protective gloves and without seeking medical attention. Over the ensuing weeks, a small reddish papule developed at the inoculation site, gradually expanding into an indurated plaque over a period of months. There were no systemic symptoms, fevers, malaise, or constitutional symptoms throughout this course. Given the chronic, indolent presentation and the patient's continued fishkeeping activity, he initially attributed the lesion to a self-limiting injury before eventually seeking dermatologic consultation.

Initial diagnostic evaluation and antifungal treatment (2023)

In March 2023, the patient underwent his first skin biopsy, the histopathology of which was reported as suspicious for a subcutaneous fungal infection. A subsequent fungal culture obtained on September 4th, 2023 grew *Phialophora* spp., establishing a presumptive diagnosis of chromoblastomycosis. On September 13th, 2023, the patient was initiated on standard antifungal therapy comprising oral

itraconazole 200 mg once daily and topical miconazole 2% cream applied every 12 hours. The regimen was continued for 48 consecutive weeks with strict adherence and regular follow-up. Despite this prolonged, guideline-concordant antifungal regimen, the lesion failed to demonstrate clinically meaningful regression. By April 2024, the plaque remained essentially unchanged in size, color, and induration, prompting reconsideration of the underlying diagnosis.

Repeat diagnostic evaluation and histopathologic re-examination (2024)

Given the clinical failure of prolonged antifungal therapy, a repeat biopsy was obtained on April 30th, 2024, with periodic acid-Schiff (PAS) staining specifically directed toward identifying residual fungal organisms. The PAS stain was negative for fungal elements, suggesting that either the antifungal therapy had successfully cleared the fungal organism or that *Phialophora* spp. was no longer the principal etiologic agent driving the persistent lesion. A further biopsy on September 2nd, 2024 was subjected to PAS staining (negative for fungi) and Ziehl-Neelsen staining (negative for acid-fast bacilli), and hematoxylin-eosin (H&E) examination revealed non-caseating tuberculoid granulomas. A confirmatory specimen on September 6th, 2024 corroborated these findings, demonstrating subcorneal pustules containing lymphocytes, plasma cells, and neutrophils within the epidermis, and dense lymphoplasmacytic infiltrates surrounding non-caseating granulomas in the dermis. The complete laboratory and histopathologic findings, with directed interpretations, are summarized in Table 2. The corresponding histopathologic features are illustrated in Figure 2.

Table 2. Sequential laboratory and histopathologic findings with directed clinical interpretations.

Investigation	Date	Result	Interpretation
Skin biopsy (H&E)	Mar 1st, 2023	Subcutaneous fungal infection suspected	Initial dx: chromoblastomycosis
Fungal culture	Sep 4th, 2023	*Phialophora* spp. isolated*	Etiologic agent of chromoblastomycosis confirmed
Repeat biopsy + PAS	Apr 30th, 2024	PAS negative for fungal elements	Suggests fungal clearance after antifungal Tx
PAS stain	Sep 2nd, 2024	Negative for fungal elements	No persistent fungal organism
Ziehl-Neelsen stain	Sep 2nd, 2024	Negative for acid-fast bacilli	Low yield (~30% sensitivity); does not exclude NTM†
H&E biopsy	Sep 2nd, 2024	Non-caseating tuberculoid granulomas	Consistent with NTM or cutaneous tuberculosis‡
Confirmatory H&E	Sep 6th, 2024	Subcorneal pustules + dense lymphoplasmacytic infiltrate around non-caseating granulomas	Pattern characteristic of *M. marinum* cutaneous infection

**Phialophora* spp. confirmed initial diagnosis of chromoblastomycosis. †Negative ZN stain does not exclude NTM infection due to low sensitivity. ‡Non-caseating granulomas favor NTM over chromoblastomycosis pathology. NTM = nontuberculous mycobacteria; PAS = periodic acid-Schiff; H&E = hematoxylin and eosin.

Physical examination at the time of diagnostic reassessment

On dedicated dermatologic examination at the time of repeat workup, the patient appeared in good general health and was alert and oriented. Vital signs were within normal limits. Cardiovascular, respiratory, abdominal, and neurologic systemic examinations were unremarkable. Dermatologic examination revealed a solitary erythematous plaque on the dorsum of the right middle finger (digiti III manus dextra), with a well-defined border, geographic shape, and dimensions of approximately 1.5 × 2 cm. The plaque exhibited mild induration without ulceration, drainage, or central necrosis. Mucous membranes, hair, and nails were unremarkable. Sweat gland function was preserved. There was no regional or distant lymphadenopathy. Sensory examination was intact, and there was no palpable nerve thickening. Sporotrichoid pattern (ascending nodular lymphangitis) was specifically sought and not identified.

Working diagnosis, differential diagnosis, and final therapeutic plan

Based on the integrated clinical picture — chronic, antifungal-refractory cutaneous lesion in a fishkeeper with documented aquatic injury, fungal culture isolation of *Phialophora* spp., subsequent histopathology demonstrating non-caseating tuberculoid granulomas, and negative PAS and Ziehl-Neelsen stains — the differential diagnosis was narrowed to nontuberculous mycobacterial infection (specifically *M. marinum*), persistent chromoblastomycosis, and cutaneous tuberculosis. Given the patient's documented aquatic exposure, antifungal failure, and characteristic histopathology, a final diagnosis of fish tank granuloma due to *Mycobacterium marinum* infection co-existing with prior or concurrent chromoblastomycosis was established. The patient was initiated on combination antimycobacterial therapy comprising rifampicin 600 mg orally once daily and ethambutol 1500 mg orally once daily, with a planned duration of 2 to 4 months and continuation for 2 months following clinical resolution. Symptomatic management included paracetamol 600 mg orally every 8 hours as needed for pain. Patient education emphasized avoidance of contaminated water exposure and meticulous wound hygiene. Detailed treatment timeline and clinical response data are presented in Table 3.

Table 3. Treatment timeline and corresponding clinical response over 30 months of follow-up.

Phase	Duration	Regimen	Clinical response
1: Antifungal therapy	Sep 2023 – Sep 2024 (48 wk)	Itraconazole 200 mg PO daily + miconazole 2% cream q12h topical	No clinical regression*
Diagnostic re-evaluation	Apr–Sep 2024	Repeat biopsies (PAS, ZN, H&E)	Non-caseating granulomas identified†
2: Antimycobacterial therapy initiation	Sep 6th, 2024	Rifampicin 600 mg PO daily + ethambutol 1500 mg PO daily	Therapy commenced
Adjunctive analgesia	As needed	Paracetamol 600 mg PO q8h PRN pain	Symptom relief
3-month follow-up	Dec 2024	Continued rifampicin + ethambutol	Visible reduction in plaque size and erythema
6-month follow-up	Mar 3rd, 2025	Continued rifampicin + ethambutol	Substantial clinical resolution‡

*Failure of prolonged guideline-concordant antifungal therapy prompted diagnostic reassessment. †Histopathologic findings re-oriented the diagnosis toward nontuberculous mycobacterial infection. ‡Dramatic clinical response to antimycobacterial therapy supported the revised diagnosis. PO = per os (oral); PRN = pro re nata (as needed).

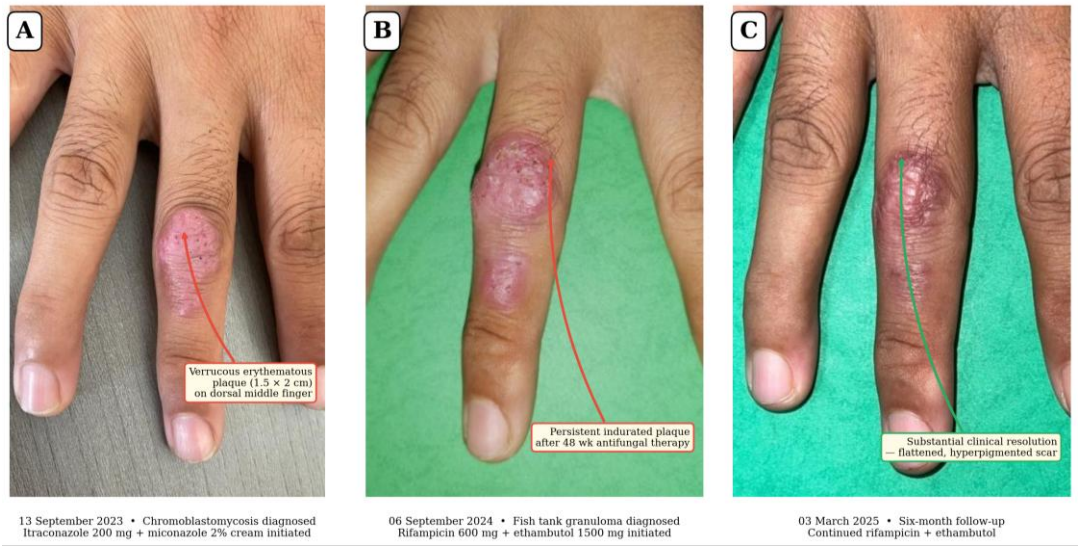

Figure 1. Serial clinical photographs of the lesion on the right middle finger (digiti III manus dextra) over the 30-month diagnostic-therapeutic course. Red arrows indicate the lesion in each panel. (A) 13th September 2023 — verrucous erythematous plaque (1.5 × 2 cm) at the time of initial diagnosis of chromoblastomycosis (*Phialophora* spp. on culture); itraconazole 200 mg daily and topical miconazole 2% were initiated. (B) 6th September 2024 — the lesion remained clinically unchanged after 48 weeks of antifungal therapy; histopathology revealed non-caseating tuberculoid granulomas led to the revised diagnosis of fish tank granuloma due to Mycobacterium marinum, and combination antimycobacterial therapy with rifampicin 600 mg and ethambutol 1500 mg daily was commenced. (C) 3rd March 2025 — substantial clinical resolution at six-month follow-up under continued rifampicin and ethambutol therapy, with the lesion flattening into a hyperpigmented residual scar (green arrow).

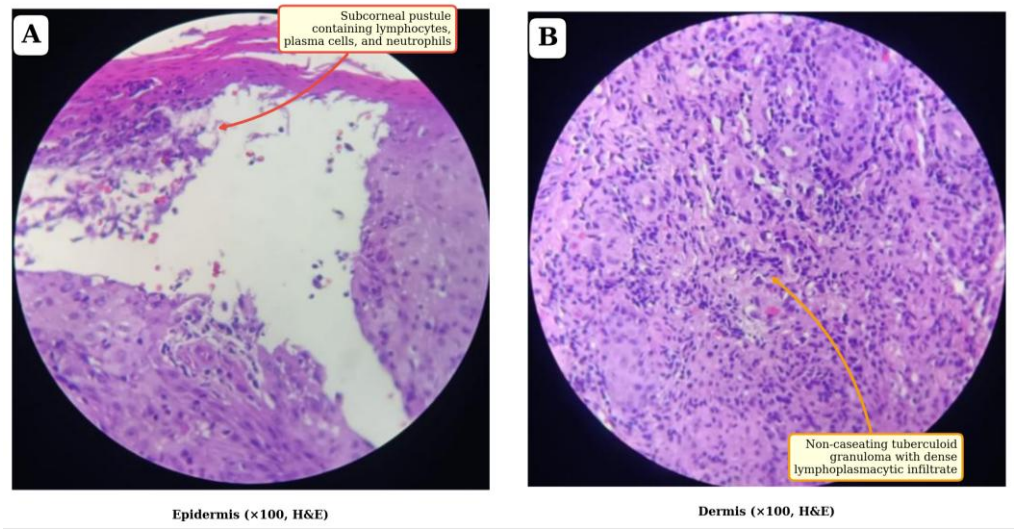

Figure 2. Histopathologic examination of the cutaneous biopsy specimen with directed annotation arrows (hematoxylin and eosin stain, ×100). (A) Epidermis — the red arrow indicates a subcorneal pustule containing a dense infiltrate of lymphocytes, plasma cells, and neutrophils, consistent with a chronic granulomatous inflammatory pattern. (B) Dermis — the orange arrow indicates a non-caseating tuberculoid granuloma surrounded by a dense lymphoplasmacytic infiltrate. The absence of caseation, sclerotic bodies (medlar bodies), and acid-fast bacilli on Ziehl-Neelsen staining, combined with the relevant aquatic exposure history and antifungal-refractory clinical course, supported the diagnosis of cutaneous *Mycobacterium marinum* infection co-existing with prior chromoblastomycosis.

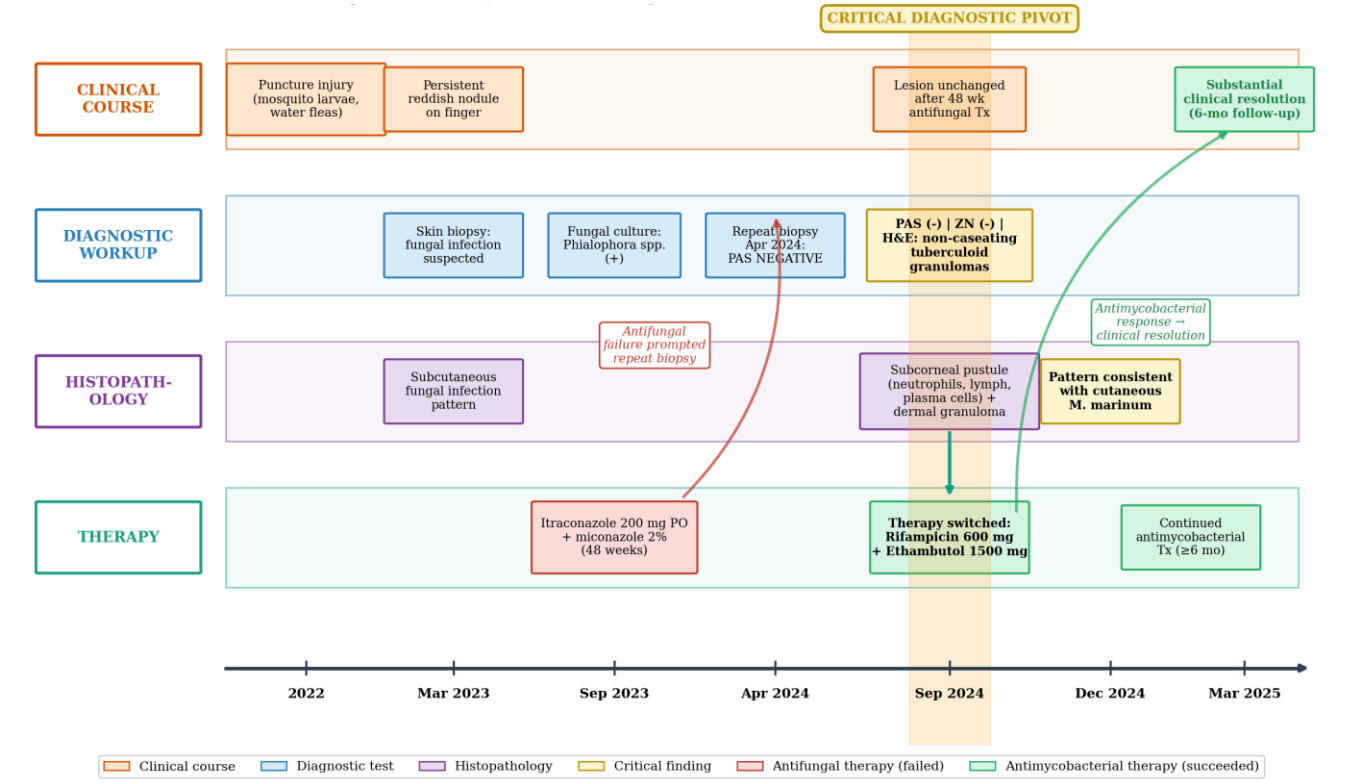

Figure 3. Comprehensive diagnostic and therapeutic milestones of the case are organized in four parallel swimlanes (clinical course, diagnostic workup, histopathology, and therapy) over the 30-month period from 2022 to March 2025. The vertical orange band marks the critical diagnostic pivot in September 2024, when repeat biopsy demonstrated non-caseating tuberculoid granulomas — combined with negative periodic acid-Schiff and Ziehl-Neelsen stains and the patient's ongoing aquatic exposure history — prompted revision of the diagnosis from chromoblastomycosis to cutaneous Mycobacterium marinum co-infection. The red curved arrow illustrates the causality flow from prolonged antifungal failure to the decision to repeat tissue sampling. The green curved arrow illustrates the rapid clinical response after therapeutic switch to rifampicin 600 mg and ethambutol 1500 mg daily, culminating in substantial lesion resolution at six-month follow-up.

3. Discussion

This case illustrates an exceptionally uncommon clinical scenario: dual-pathogen co-infection involving *Mycobacterium marinum* and a dematiaceous fungus (*Phialophora* spp.) within a single chronic cutaneous lesion. Although individual cases of *M. marinum* infection and chromoblastomycosis are well-documented, true co-infection of both organisms in the same anatomic site is rarely reported in the international literature.[9,13] The diagnostic and therapeutic complexity arises from the substantial morphologic and histopathologic overlap between these conditions, the limited sensitivity of conventional staining methods, and the divergent treatment regimens required for each pathogen. The longitudinal course documented in this case — with clinical failure of 48 weeks of guideline-concordant antifungal therapy followed by rapid clinical resolution after initiation of antimycobacterial therapy — provides compelling evidence of dual pathogenic involvement and highlights an underappreciated entity in tropical dermatology, as outlined in Table 4.

Table 4. Comparison of the present case with previously reported cases of *M. marinum* mimicking chromoblastomycosis or related diagnostic dilemmas.

Reference/case	Patient	Initial diagnosis	Final diagnosis	Outcome/lesson
Present case (2026)	31 y, M, Indonesian, fishkeeper	Chromoblastomycosis (*Phialophora* spp.)	*M. marinum* + chromoblastomycosis co-infection	Antimycobacterial Tx → resolution at 6 mo
Bezerra et al., 2020	Adult male, immunocompromised	Chromoblastomycosis suspected	Disseminated *M. marinum* simulating chromomycosis	Recognition of mimicry critical for treatment
Hui et al., 2019	Middle-aged adult, freshwater exposure	Chronic granulomatous lesion	Confirmed *M. marinum* (culture +)	Combination Rif + Eth + clarithromycin → resolution
Brooks et al., 2014 (series)	Multiple hand cases	Variable initial dx	*M. marinum* hand infection	Hand involvement common; surgical adjunct sometimes needed
Demitsu et al., 2009	Adult with atopic dermatitis	Chronic nodular lesion	Recurrent fish tank granuloma	Underlying skin disease may predispose to recurrence

Tx = treatment; Rif = rifampicin; Eth = ethambutol. The present case is distinguished by documented dual-pathogen involvement with sequential antifungal failure and antimycobacterial response.

Mycobacterium marinum is recovered from aquariums, swimming pools, fish ponds, and natural bodies of water worldwide, with reservoirs including freshwater fish, dolphins, shrimp, and water fleas — the same vectors implicated in our patient's exposure history.[1,2] The infection is recognized as an occupational hazard for aquaculture workers, marine biologists, fish handlers, ornamental fish enthusiasts, and aquarium maintenance personnel, and an increased incidence is observed among individuals engaged in fishkeeping as a hobby and those participating in marine tourism.[3,15] Inoculation typically occurs through traumatic injury (puncture wounds, abrasions, lacerations) sustained during contact with contaminated water or aquatic organisms; less commonly, infection may occur through pre-existing skin defects exposed to aquatic environments. Our patient's profile — chronic fishkeeping with hands-on collection of aquatic feed organisms (mosquito larvae and water fleas) and unaddressed traumatic injury — represents a paradigmatic exposure scenario predisposing to *M. marinum* inoculation.

Chromoblastomycosis, in contrast, is typically associated with traumatic inoculation of dematiaceous fungi from soil, decaying vegetation, or organic plant matter, with predilection for agricultural and forest workers in tropical regions.[6,8] Indonesia, with its tropical climate, extensive coastline, robust aquaculture sector, and traditional agricultural practices, represents a region where exposure to both pathogens is geographically and occupationally feasible. The convergence of risk factors in our patient — prolonged aquatic exposure with mosquito larvae handling, which may carry environmental dematiaceous fungi adherent to aquatic surfaces — provides a plausible exposure framework for true co-infection. The aquatic ecology of *Phialophora* species, while less well-characterized than soil ecology, has been documented in environmental studies of aquatic biofilms and submerged organic substrates.[7,16]

The diagnostic pitfall illustrated by this case stems from the considerable morphologic and histopathologic overlap between *M. marinum* infection

and chromoblastomycosis. Both conditions present as chronic, indolent, slowly progressive cutaneous lesions on distal extremities, with verrucous, nodular, plaque, or ulcerative morphology. Both predominantly affect immunocompetent hosts and may persist for months to years before diagnosis. Histopathologically, *M. marinum* can produce non-caseating tuberculoid granulomas indistinguishable from those of chromoblastomycosis when classical sclerotic bodies are sparse or absent.[11,17] Conventional Ziehl-Neelsen staining for *M. marinum* achieves sensitivity of only approximately 30%, providing limited diagnostic value when negative.[1,4] Mycobacterial culture, while more sensitive (70-80%), requires specialized laboratory facilities and 2-6 weeks for definitive growth. As shown in Table 2 and Figure 3, our patient's diagnostic odyssey illustrates how reliance on initial fungal culture and conventional staining can establish a single-pathogen diagnosis while masking concurrent or subsequent mycobacterial co-infection. The decision to pursue a repeat biopsy after antifungal failure proved pivotal in establishing the correct diagnosis.

The histopathologic finding of non-caseating tuberculoid granulomas in our patient's repeat biopsies represents the diagnostic turning point. Non-caseating granulomas are characteristic of nontuberculous mycobacterial infections, sarcoidosis, foreign-body reactions, and certain fungal infections, but are not typical of chromoblastomycosis, which classically demonstrates pseudoepitheliomatous hyperplasia, mixed inflammatory infiltrates, neutrophilic abscesses, and pigmented sclerotic bodies.[6,11] The presence of subcorneal pustules with neutrophilic infiltrates, dense lymphoplasmacytic perigranulomatous inflammation, and absence of sclerotic bodies in our patient's specimen pattern is highly characteristic of cutaneous mycobacterial infection. The differential of granulomatous skin disease in this clinical context includes cutaneous tuberculosis (excluded by negative ZN stain and absence of caseation), atypical mycobacterial infection (supported by aquatic exposure and antifungal failure), and sarcoidosis (excluded by absence of systemic features).[11,17,18] The convergent histopathologic, clinical, and exposure data established the working diagnosis of *M. marinum* co-infection. The corresponding histopathologic features in our patient — subcorneal pustules with neutrophilic infiltrates in the epidermis and non-caseating granulomas with dense lymphoplasmacytic infiltrate in the dermis — are illustrated in Figure 2.

The most clinically informative aspect of this case is the dramatic clinical response to antimycobacterial monotherapy (rifampicin and ethambutol) following 48 weeks of antifungal therapy that failed to produce resolution. This therapeutic dichotomy provides strong indirect evidence that *M. marinum* was the dominant pathogen driving lesional persistence, even if the initial fungal culture authentically identified *Phialophora* spp. as a co-pathogen. Several explanatory hypotheses warrant consideration: (1) the antifungal therapy may have successfully cleared *Phialophora* spp. while the unrecognized *M. marinum* infection persisted; (2) the two pathogens may have been simultaneously present from inoculation, with antifungal therapy effecting partial control while antimycobacterial therapy provided definitive resolution; or (3) *Phialophora* spp. may have represented contamination or secondary colonization rather than primary infection, with *M. marinum* representing the true etiologic agent throughout. The standard treatment for fish tank granuloma involves rifampicin 600 mg once daily and ethambutol 25 mg/kg once daily for 1-2 months following clinical resolution, with minimum duration of 3 months.[1,14,19] Alternative regimens incorporate clarithromycin, doxycycline, moxifloxacin, or rifabutin in cases of intolerance or treatment failure.[5,20]

Although our diagnostic approach was constrained to histopathologic staining and conventional fungal culture, modern molecular diagnostic methods have revolutionized the identification of cutaneous mycobacterial and fungal infections. Polymerase chain reaction (PCR) targeting the hsp65, rpoB, or 16S-23S internal transcribed spacer regions enables rapid

species-level identification of nontuberculous mycobacteria, including *M. marinum*, even when traditional culture is negative or contaminated.[21,22] Panfungal and panmycobacterial PCR assays performed directly on biopsy tissue or fixed paraffin-embedded blocks can definitively establish etiology in 65-80% of cases reported in recent literature. Similarly, molecular characterization of dematiaceous fungi has expanded the recognized species list within the genus *Phialophora* and identified novel pathogens previously misclassified.[8,16] Fungal DNA sequencing of internal transcribed spacer 1 and 2 (ITS1/ITS2) and translation elongation factor 1-alpha (TEF-1α) genes provides reliable species-level identification, particularly when phenotypic characteristics overlap. The absence of subsequent molecular confirmation in our case represents a limitation that may be relevant for laboratories in resource-constrained settings considering similar diagnostic algorithms.

M. marinum has historically been considered susceptible to several antimicrobial agents, but emerging evidence indicates that some strains harbor genetic determinants conferring reduced susceptibility. The organism is intrinsically resistant to most beta-lactam antibiotics, aminoglycosides, and chloramphenicol due to gene-encoding mechanisms.[1,5] Rifampicin resistance, although rare, has been documented and is associated with mutations in the rpoB gene encoding the beta subunit of RNA polymerase. Clarithromycin and azithromycin retain excellent in vitro activity against most clinical isolates, while doxycycline, minocycline, and trimethoprim-sulfamethoxazole demonstrate variable but generally good activity. The rifampicin–ethambutol regimen selected in our case followed standard recommendations,[14,19] and the rapid clinical response within six months supported retention of this regimen. In severe, sporotrichoid-pattern, or deep-tissue extension cases, three-agent combination therapy is recommended; treatment duration ranges from 3 to 12 months, with most authorities recommending continuation for at least 1 to 2 months after complete clinical resolution to prevent relapse.[5,20,23]

The chronic indurated nodular lesion on the dorsal hand of an individual with aquatic exposure demands a thorough differential diagnosis extending beyond *M. marinum* and chromoblastomycosis. Sporotrichosis, caused by *Sporothrix schenckii* sensu lato, classically produces ascending nodular lymphangitis (sporotrichoid pattern) but can also present as localized verrucous or plaque-form lesions indistinguishable from the present case.[6,15] Cutaneous tuberculosis, particularly lupus vulgaris and tuberculosis verrucosa cutis variants, can mimic both organisms. Atypical mycobacterial infections beyond *M. marinum* — including *M. abscessus*, *M. chelonae*, *M. fortuitum*, *M. ulcerans*, and *M. avium* complex — can present similarly with different treatment implications.[15,22] Phaeohyphomycosis caused by other dematiaceous fungi, leishmaniasis in endemic regions, and sarcoidosis with cutaneous manifestations should be entertained. The presence of non-caseating granulomas does not specifically distinguish among these mimics; the clinical context, additional histopathologic features, and treatment response collectively guided the final diagnosis in our patient.

This case provides several lessons of broad clinical relevance. First, the diagnosis of chromoblastomycosis should not preclude consideration of nontuberculous mycobacterial co-infection, particularly when initial antifungal therapy fails. As demonstrated in Tables 3 and 4, repeated tissue sampling with directed staining is warranted when treatment response is inadequate. Second, comprehensive aquatic exposure history — including occupational fishing, aquarium maintenance, marine tourism, recreational fishing, and freshwater contact — should be systematically elicited and documented. Third, mycobacterial cultures require 2-6 weeks for results, which can substantially delay diagnosis; integration of molecular diagnostic platforms shortens time-to-diagnosis when conventional culture is negative.[21,22] Fourth, patient education on aquatic exposure prevention is paramount. The Centers for Disease Control and

Prevention recommends waterproof gloves when handling aquaria, fishponds, or aquatic feed organisms; prompt cleaning and antiseptic treatment of any cuts sustained during such activities; and avoidance of aquatic contact with open wounds.[3,17] Fifth, in aquaculture and ornamental fishkeeping, sanitation, disinfection, and culling of carrier fish are recommended preventive strategies. Ultraviolet light exposure and chlorine concentrations of 5-10 ppm reduce environmental *M. marinum* loads, although the organism is more chlorine-resistant than non-mycobacterial pathogens.

The strengths of this case report include detailed clinical, histopathologic, and therapeutic documentation across a 30-month longitudinal course, providing clear evidence of dual-pathogen involvement through sequential antifungal failure and antimycobacterial response. Several limitations should be acknowledged. First, molecular confirmation of *M. marinum* was not performed; the diagnosis was supported by histopathology, exposure history, antimycobacterial response, and exclusion of cutaneous tuberculosis. Second, the persistence of *Phialophora* spp. in tissue at the time of antimycobacterial treatment initiation could not be definitively demonstrated, raising the possibility that the fungal organism had been cleared by prior antifungal therapy. Third, the absence of immunological assessment precluded ruling out subtle deficits predisposing to dual cutaneous infection. Future research priorities include molecular surveillance of cutaneous mycobacterial infections in aquatic-exposed populations, prospective evaluation of empiric antimycobacterial therapy in patients with chromoblastomycosis-like presentations who fail antifungal therapy, and investigation of immunological substrates that may permit dual-pathogen colonization.[14,21]

Beyond the individual patient, this case underscores broader public health and occupational health implications. The aquaculture industry, ornamental fish trade, and marine tourism sectors expose substantial populations to *M. marinum* and related environmental mycobacteria. Indonesia, with its extensive coastline, robust aquaculture sector, and growing ornamental fish industry, represents an at-risk environment for these infections. Public health surveillance of cutaneous mycobacterial infections in aquaculture workers, fish handlers, and aquarium employees remains underdeveloped in many low- and middle-income countries, leading to underdiagnosis.[5,15] Educational interventions targeting these populations should emphasize personal protective equipment (waterproof gloves), prompt wound care, recognition of warning signs of cutaneous infection, and timely medical evaluation. Healthcare provider training should include recognition of typical *M. marinum* presentations, the diagnostic algorithm for chronic cutaneous nodular lesions, and appropriate empirical therapeutic approaches in suspected cases. The economic and social burden of misdiagnosis or delayed diagnosis extends beyond the individual patient, encompassing prolonged disability, repeated diagnostic procedures, ineffective treatment costs, and potential complications including dissemination in immunocompromised hosts.

The pathogenesis of dual cutaneous co-infection between *Mycobacterium marinum* and chromoblastomycosis (*Phialophora* spp.) merits mechanistic discussion. Both pathogens are environmental organisms that gain access to dermal tissue through compromised skin barrier integrity, typically following minor trauma. Once inoculated, *M. marinum* is internalized by tissue macrophages, where the organism's lipid-rich cell wall and unique pathogenicity factors permit intracellular persistence and granuloma formation.[1,4,17] In contrast, dematiaceous fungi proliferate as sclerotic bodies (medlar bodies) in the dermis and epidermis, eliciting a mixed inflammatory response that includes pseudoepitheliomatous hyperplasia, microabscess formation, and chronic granulomatous inflammation.[6-8] The simultaneous presence of both pathogens in a single anatomic site may create a complex immunological microenvironment in which

the cellular immune response to one organism modulates susceptibility to the other. Animal model studies have demonstrated that *M. marinum* infection induces a Th1-skewed response with interferon-gamma production and macrophage activation, while chromoblastomycosis is associated with a more variable Th17/Th2-mediated response. The interplay between these distinct immune polarizations may permit dual pathogen survival and chronic infection.[11,15]

Although the diagnosis of cutaneous *M. marinum* infection rests primarily on histopathology, culture, and clinical correlation, adjunctive imaging modalities can provide valuable supportive information when deep tissue extension or tenosynovitis is suspected. High-frequency ultrasonography reveals characteristic hypoechoic deep dermal collections and may identify subclinical extension into tendon sheaths or joint spaces.[18] Magnetic resonance imaging (MRI) is the imaging modality of choice when deep tissue or tenosynovial involvement is clinically suspected, demonstrating T2-hyperintense collections, peripheral enhancement on contrast administration, and adjacent soft tissue edema. The Brooks et al. case series of *M. marinum* hand infections highlighted that approximately 25% of cases involve deep tissue extension to flexor tendon sheaths, occasionally requiring surgical debridement in addition to antimicrobial therapy.[10,18] Although our patient's lesion was confined to superficial dermis without clinical evidence of tenosynovitis or deep extension, MRI imaging would be considered if clinical progression occurred during therapy or if the lesion failed to resolve as expected. Dermoscopy of cutaneous mycobacterial infections may reveal characteristic features including yellow-orange globules corresponding to granulomatous infiltration, although these findings are not pathognomonic and should be interpreted in conjunction with histopathology.

The diagnostic workup of chronic cutaneous nodular lesions in resource-limited settings such as parts of Indonesia must balance diagnostic accuracy with cost-effectiveness. Conventional histopathology and basic special stains (PAS, Ziehl-Neelsen, Grocott methenamine silver) remain the cornerstone of diagnosis and are widely available even in district hospitals. Mycobacterial culture, while more sensitive than conventional stains, requires specialized BACTEC or MGIT systems with biosafety level 2 facilities and turnaround times of 2-6 weeks, which may not be feasible in many regional centers.[14,19,21] Molecular diagnostics (PCR, sequencing) offer faster turnaround but require capital investment and trained personnel. A pragmatic diagnostic algorithm for resource-limited settings might include: (1) initial biopsy with H&E and PAS staining; (2) fungal culture if PAS positive or clinical suspicion remains high; (3) repeat biopsy with Ziehl-Neelsen and acid-fast bacilli (AFB) staining if antifungal therapy fails or if granulomatous histopathology is observed; (4) referral for mycobacterial culture and molecular testing at a tertiary center if *M. marinum* or other NTM is suspected; and (5) empiric antimycobacterial therapy in clinically high-suspicion cases pending definitive identification.[1,4,5] Such algorithms could substantially reduce diagnostic delays while remaining feasible within typical resource constraints.

The case described herein argues for several practical recommendations to dermatologists, infectious disease specialists, and primary care providers practicing in regions with significant aquaculture, ornamental fishkeeping, or marine tourism populations. First, a comprehensive aquatic exposure history should be a standard component of the dermatologic interview for any patient presenting with chronic cutaneous nodular lesions on the distal extremities. Second, when initial fungal culture identifies a dermatologic pathogen and standard antifungal therapy is initiated, periodic clinical reassessment at 3-month intervals should evaluate treatment response; failure to demonstrate clinical regression by 6 months should prompt reconsideration of diagnosis and consideration of repeat biopsy.[6,7,9] Third, repeat biopsy specimens should routinely include both PAS staining (for fungal

organisms) and Ziehl-Neelsen staining (for acid-fast bacilli), as well as H&E examination for non-caseating granulomas. Fourth, in patients with characteristic exposure histories and antifungal-refractory courses, empiric antimycobacterial therapy may be reasonable while awaiting culture confirmation, particularly when molecular diagnostic testing is unavailable. Fifth, multidisciplinary collaboration involving dermatology, infectious diseases, pathology, and microbiology should be encouraged for these complex cases. Sixth, formal documentation of *M. marinum*/chromoblastomycosis co-infection cases in the regional medical literature is essential to characterize the true epidemiology and clinical features of this entity, which remains underrepresented in published case series.[9,13,17]

4. Conclusion

This case of co-infection between *Mycobacterium marinum* and chromoblastomycosis (*Phialophora* spp.) in a 31-year-old fishkeeper highlights critical diagnostic and therapeutic principles in tropical dermatology. The patient's antifungal-refractory course over 48 weeks of itraconazole and miconazole, followed by rapid clinical resolution after rifampicin-ethambutol antimycobacterial therapy, provides compelling evidence of dual pathogenic involvement and underscores the necessity of repeat histopathology with directed staining when initial therapy fails. Clinicians caring for patients with chronic cutaneous nodular lesions and aquatic exposure history must maintain a high index of suspicion for nontuberculous mycobacterial infection, particularly when initial fungal cultures and antifungal therapy do not achieve resolution. The integration of clinical, histopathologic, and exposure data — together with consideration of molecular diagnostic adjuncts where available — enables timely and accurate diagnosis. This report contributes to the growing literature on cutaneous co-infection, advances our understanding of diagnostic pitfalls in mimicking conditions, and emphasizes the importance of patient education on aquatic exposure prevention, particularly within Indonesia's expanding aquaculture and ornamental fishkeeping populations.

5. References

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