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Multidrug-resistant *Mycobacterium abscessus* infection in an anophthalmic socket treated with bedaquiline on a compassionate use basis: A case report

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ABSTRACT

Purpose: To explore the management of a rare ophthalmic infection caused by a multi-resistant strain of *Mycobacterium abscessus* in the anophthalmic cavity of a patient with a history of multiple eye surgeries.
Observations: A 60-year-old woman with a history of multiple ocular complications, culminating in the enucleation of the eye and subsequent dermograft implant, developed a resistant infection in the anophthalmic cavity. The infection persisted despite various local interventions and broad-spectrum systemic antibiotic treatments. Resolution of the infection was only achieved after precise diagnosis and the implementation of intensive treatment, which included a specific combination of antibiotics and appropriate surgical debridement of the anophthalmic cavity.
Conclusions and importance: This case highlights the complexity in managing ophthalmic infections caused by non-tuberculous mycobacteria. It underscores the importance of a multidisciplinary and personalized treatment approach, as well as the need to develop specific guidelines for ophthalmic infections caused by rapidly growing mycobacteria.

1. Introduction

Non-tuberculous mycobacteria are a rare cause of ophthalmic infection following surgery or ocular trauma.[1–7] The visual prognosis of the affected eye is usually very poor, as evidenced in various case series.[2–5] The reasons for this poor visual prognosis include multiple factors: the long incubation period, which can vary from a few days to several months (median of 2 months)[6,8]; the difficulty in making an accurate diagnosis; the significant antimicrobial resistance of these microorganisms, particularly *Mycobacterium abscessus* subsp. *abscessus*[9,10]; and therapeutic failure against available treatment regimens. Unlike pulmonary infections, most ophthalmic infections are of exogenous origin and are not associated with an underlying immunosuppressive process. The use of steroids represents the only recognized risk factor, in addition to trauma, foreign body presence, or previous ocular surgery.[6]

In this clinical case, we describe an infection of the anophthalmic cavity caused by multi-resistant *M. abscessus* in a patient with numerous previous surgical interventions in the affected area. This entity is rare even within the context of ophthalmic infections in published series.[2,6,7,11] Additionally, the use of bedaquiline in a compassionate use regimen is detailed, given the absence of other classic treatment options.

2. Case report

A 60-year-old woman with a personal history of dyslipidemia who presented with choroidal melanoma in the left eye was treated with episcleral brachytherapy in 2011, which led to ocular ischemia and the subsequent development of neovascular glaucoma. Subsequent complications from the glaucoma, including severe pain and complete vision loss, necessitated the enucleation of the affected eye. Initially, a hydroxyapatite internal implant coupled with an external ocular prosthesis was used for orbital reconstruction. However, she experienced multiple episodes of membranous conjunctivitis, compelling the oculoplastic surgeon to remove the internal prosthesis and perform a dermofat graft. Postoperatively, the patient faced recurrent conjunctivitis and orbital cellulitis, which led to the use of both topical steroids and topical and

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systemic antibiotics.

After nine years of recurrent conjunctivitis, an infection in the anophthalmic cavity was diagnosed, characterized by marked inflammatory signs and necrosis. Despite local treatments, including intracavitary triamcinolone injections, successive washes with autologous serum, and dexamethasone and tobramycin eye drops, as well as multiple cycles of oral antibiotics (doxycycline, amoxicillin-clavulanate, cotrimoxazole, and levofloxacin), the clinical course worsened. Shortly thereafter, the patient experienced palpebral rupture and copious purulent discharge. (Fig. 1).

Following the isolation of *Achromobacter xylosoxidans* from the exudate culture and confirmation of its susceptibility to ceftazidime, directed treatment with intravenous ceftazidime was administered, with no clinical improvement. Subsequently, a rapidly growing mycobacterium was identified in a pus exudate, preliminarily identified as *Mycobacterium abscessus complex* (Fig. 2). Therefore, hospital admission was decided to initiate intensive treatment after surgical debridement of the anophthalmic cavity.

Comprehensive orbital debridement was performed, extending to the periosteum in selected areas to ensure the complete removal of all necrotic tissue, which was notably abundant. This procedure ensured the exposure of vascularized tissue throughout the orbital locations. After the surgical intervention, complementary tests were conducted, revealing normal levels of C-reactive protein and procalcitonin. Additionally, computed tomography of the orbits showed no evidence of bone involvement or regional dissemination. Distant involvement was also excluded based on chest radiography and repeated physical examinations.

Pending identification at the subspecies level, empirical combined intravenous treatment was initiated with amikacin at 12.5 mg/kg (750 mg), imipenem 1 g every 8 hours, and tigecycline 50 mg every 12 hours, along with oral azithromycin 500 mg.

During the admission, the patient had digestive intolerance attributable to the use of tigecycline, which led to its suspension due to the onset of hepatitis. Due to the lack of availability of the antibiogram of the isolate, tigecycline was replaced with intravenous cefoxitin 2 g every 8 hours. At the patient's request, she was discharged home after 19 days of intravenous treatment, without yet having the definitive microbiological identification. Pending the results of phenotypic resistance, a quadruple oral therapy composed of azithromycin 500 mg every 24 h, moxifloxacin 400 mg every 24 h, linezolid 600 mg every 12 h, and rifabutin 300 mg every 24 h was maintained.

The patient showed good initial progress during outpatient follow-up. However, after receiving the final results of the microbiological sensitivity test, which revealed a multi-resistant strain, bedaquiline was requested for off-label use. Table 1. Treatment was maintained for 6 months with linezolid at a dose of 600 mg every 24 h, azithromycin 500 mg every 24 h, and bedaquiline according to the usual schedule (400 mg every 24 h for the first two weeks, followed by 200 mg three times a week). Rifabutin was withdrawn due to hepatic toxicity.

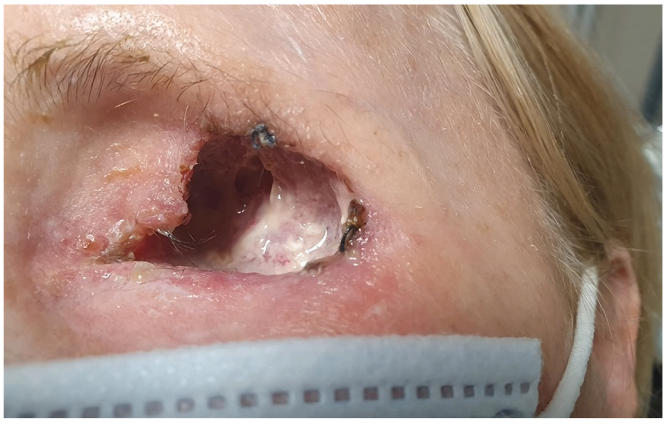

Fig. 1. Infection of the anophthalmic cavity with marked presence of purulent eschar, upper eyelid rupture, and periorbital cellulitis.

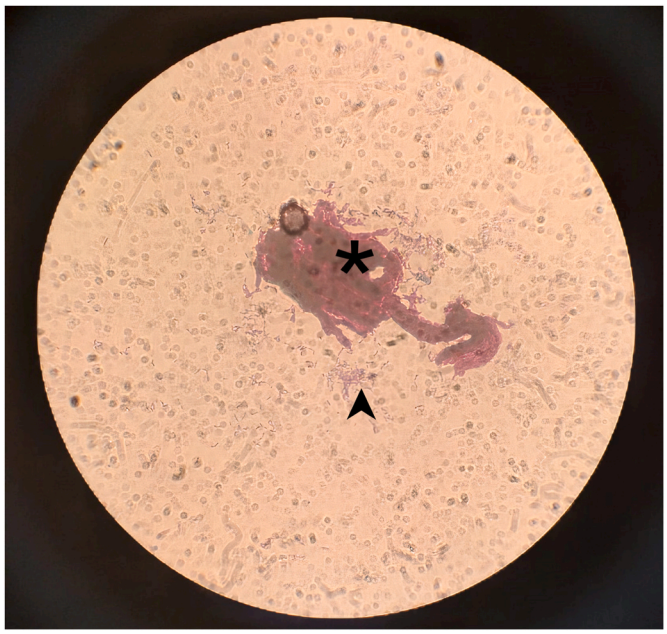

Fig. 2. Growth of rapidly growing mycobacterial colonies on Chocolate Agar, indicated by an arrowhead. Acid-fast bacteria, stained with Ziehl-Neelsen staining and highlighted by an asterisk, exhibit clustering in cords—a characteristic pattern common in M. abscessus. Detritus is also visible in the background.

Table 1

Amikacin MIC >64 μg/mL.	Resistant (A1408G mutation in rrs gene).
Cefoxitin MIC 32 μg/mL.	Susceptible with Increased Exposure.
Ciprofloxacin MIC >4 μg/mL.	Resistant.
Clarithromycin MIC 0.5 μg/mL.	Inducible resistance (T28 genotype in erm gene).
Doxycycline MIC >16 μg/mL.	Resistant.
Tigecycline MIC 0.5 μg/mL.	No breakpoints have been established by the CLSI.
Imipenem MIC 32 μg/mL.	Susceptible with Increased Exposure.
Linezolid MIC 16 μg/mL.	Susceptible with Increased Exposure.
Moxifloxacin MIC >8 μg/mL.	Resistant.
Trimethoprim/Sulfamethoxazole MIC >8/152 μg/mL.	Resistant
Tobramycin MIC >16 μg/mL.	Resistant.

Antimicrobial Susceptibility Testing for our isolate of *Mycobacterium abscessus* subsp. *abscessus*. Susceptibility interpretation according to M24-A2, 'Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes,' as per the Clinical and Laboratory Standards Institute (2011).

The patient showed satisfactory clinical improvement during follow-up (Fig. 3). Once the treatment was completed, no signs of local recurrence were observed, allowing the placement of an ocular prosthesis with a good aesthetic result.

3. Discussion

The primary challenge in managing ophthalmic infections caused by non-tuberculous mycobacteria lies in the misidentification of the causative agent. However, with the advent of advanced diagnostic tools, such misidentifications are becoming less frequent. In our case, the repeated isolation of *A. xylosoxidans* initially led to an inappropriate treatment with ceftazidime, resulting in a delay in adopting the correct

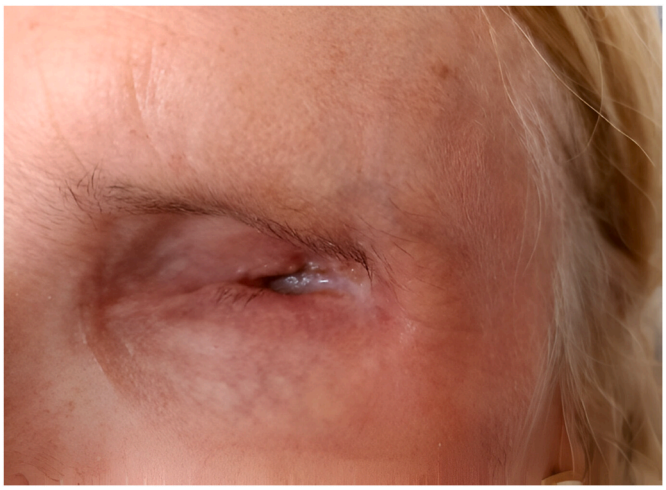

Fig. 3. Positive progression of the infection during the maintenance phase of treatment, illustrating significant healing of the orbital tissues. The image highlights reduced inflammation of the eyelid, periorbital cutaneous tissue, and, particularly, the orbital cavity. It shows resolution of necrotic tissue (eschar) and inflammatory exudate.

therapeutic strategy. Clinicians should consistently consider the possibility of non-tuberculous mycobacteria in the differential diagnosis following treatment failure, especially when the initial treatment seems appropriate. This is crucial due to the potential for faster-growing microorganisms to obscure the presence of non-tuberculous mycobacteria. In our case, it is impossible to determine the exact moment when the *M. abscessus* infection occurred due to the poor progression following multiple orbital interventions, as well as the prolonged latency period described in the literature between surgical contamination and the development of infection by this microorganism.

Unlike pulmonary infections caused by rapidly growing mycobacteria, there is currently no standard treatment for ophthalmic infections caused by these pathogens. The literature consulted offers a limited and heterogeneous number of cases, reflecting the variety of ocular and annexed tissues susceptible to infection by these mycobacteria. Generally, cases have been managed with a combination of local antimicrobial treatment, systemic therapy, and surgical debridement.[3,5,7,11–14] However, this strategy faces challenges such as the need for prolonged intravenous treatment, high economic cost, limited availability of oral options, and low tolerability of the drugs used.[15,16]

Among the agents with proven activity against *M. abscessus*, only macrolides and amikacin have unequivocally demonstrated a relationship between in vitro activity and clinical efficacy.[10] Macrolides are considered the cornerstone of treatment; however, most isolates show activity in the erm gene, which causes inducible resistance to these drugs. Most authors argue that amikacin is the second most important drug in a combined regimen. Other first-line drugs include tigecycline, imipenem, cefoxitin, and linezolid. There is sufficient evidence of activity, and these can be used as part of the treatment regimen: clofazimine, tedizolid, moxifloxacin or gatifloxacin, doxycycline or omadacycline, cotrimoxazole, rifabutin, and bedaquiline. There is scarce clinical evidence for the recommendation of combining beta-lactams, but there is evidence of synergy between imipenem with cefoxitin, ceftaroline and ceftazidime, as well as imipenem with the beta-lactamase inhibitors avibactam and relebactam.[9,10,17–23]

The treatment is divided into an induction phase and a maintenance phase, the duration of which is a subject of debate even in pulmonary infections, where the evidence is more robust.[15,17] The necessary time in the initial phase varies between 2 and 16 weeks, recommending completion of up to 4–6 months in the maintenance phase.[12,24] The use of at least 3 or 4 compounds in the initial phase is recommended, excluding the use of macrolides in cases of inducible resistance, followed by 2 or 3 drugs in the continuation phase.[17] The macrolide can be used for its anti-inflammatory effect, although this practice is based on experiences with pulmonary infections and its extrapolation to ophthalmic cases is uncertain. Table 2.

In the clinical case presented, an initial extended treatment phase was attempted, but the patient declined to extend her hospital stay and

Table 2

Initial Phase	Treatment Duration: 2–16 weeks
Macrolide Susceptibility	Utilize at least 3 categories from the following drugs. Always choose a combination that includes A and B, whenever possible: A. Azithromycin or Clarithromycin B. Amikacin C. Imipenem or Cefoxitin, or combinations based on Imipenem with Cefotixin, Imipenem with Ceftaroline or Ceftazidime, or Imipenem with Ceftazidime-Avibactam. D. Tigecycline or Omadacycline E. Linezolid or Tedizolid F. Clofazimine G. Bedaquiline H. Moxifloxacin or Gatifloxacin
Macrolide Resistance or Inducible Resistance	Utilize 4 categories from the following drugs. Always choose a combination that includes A, B, and C, whenever possible: A. Amikacin B. Imipenem or Cefoxitin, or combinations based on Imipenem with Cefotixin, Imipenem with Ceftaroline or Ceftazidime, or Imipenem with Ceftazidime-Avibactam. C. Tigecycline or Omadacycline D. Linezolid or Tedizolid E. Clofazimine F. Bedaquiline G. Moxifloxacin or Gatifloxacin
Consolidation Phase	Continue treatment for at least 6 months.
Macrolide Susceptibility	Utilize 2 or 3 categories from the following drugs. Always choose a combination that includes A, whenever possible: A. Azithromycin or Clarithromycin B. Omadacycline or Doxycycline C. Linezolid or Tedizolid D. Clofazimine E. Bedaquiline or Bedaquiline with Rifabutin F. Moxifloxacin or Gatifloxacin G. Trimethoprim/Sulfamethoxazole
Macrolide Resistance or Inducible Resistance	Utilize at least 2 categories from the following drugs: A. Omadacycline or Doxycycline B. Linezolid or Tedizolid C. Clofazimine D. Bedaquiline or Bedaquiline with Rifabutin E. Moxifloxacin or Gatifloxacin F. Trimethoprim/Sulfamethoxazole
Standard Dosages: • Azithromycin: 250mg or 500mg daily • Clarithromycin: 500mg twice a day • Amikacin: 10–15mg/kg per day • Tigecycline: 50mg–100mg per day divided into 2 doses • Omadacycline: 300mg once a day • Doxycycline: 100mg twice a day • Linezolid: 600mg once or twice a day (use every 24 hours in maintenance phase) • Tedizolid: 200mg once a day • Imipenem: 2–3g per day divided into 2–4 doses • Cefoxitin: 6–12g per day divided into 2–3 doses • Ceftaroline: 600mg twice a day • Ceftazidime: 2g twice a day • Ceftazidime-Avibactam: 2g/0.5g twice a day • Clofazimine: 100–200mg per day • Bedaquiline: 400mg per day for 2 weeks, then 200mg three times a week • Rifabutin: 300mg per day • Moxifloxacin: 400mg per day • Gatifloxacin: 200–400mg per day • Trimethoprim/Sulfamethoxazole: 160/800mg twice a day	

Recommended Treatment Regimen for Pulmonary Infections Caused by *Mycobacterium abscessus*.

there was no availability of home-based intravenous antimicrobial therapy, resulting in a suboptimal oral regimen. After confirming the pathogen's multi-resistance, compassionate use of bedaquiline was authorized, initially in combination with rifabutin, based on the synergy described in animal studies. However, rifabutin was quickly discontinued due to digestive intolerance, hepatitis, and concerns about pharmacological interactions with linezolid, whose effectiveness was already compromised by the high MIC of the microbiological isolate.

In our case, bedaquiline was chosen for its nearly universal in vitro activity against all rapidly growing mycobacteria and the lack of suitable oral alternatives for our patient: omadacycline was not considered due to a history of tigecycline-induced hepatitis, and clofazimine was discarded because of its lower likelihood of sensitivity, given the reference laboratory's inability to provide a sensitivity study for both antimicrobials.

Bedaquiline has a unique mechanism of action, targeting the inhibition of the c subunit of ATP synthase in the genus *Mycobacterium* spp., and possesses bactericidal activity at any stage of bacillus replication. Although it is FDA-approved exclusively for the treatment of pulmonary infections by multidrug-resistant tuberculosis as part of a treatment regimen in the absence of other valid alternatives, bedaquiline also demonstrates high in vitro activity against a broad group of non-tuberculous mycobacteria, including *M. avium*, *M. leprae*, and, notably, rapidly growing mycobacteria, where other treatment options are lacking.

Nevertheless, the use of bedaquiline should be approached with caution and strictly supervised by experienced physicians, such as infectious disease specialists or internists. In addition to not being approved for this specific indication, the drug has been linked to an increased mortality rate compared to placebo and requires monitoring for cardiac toxicity due to potential QT interval prolongation.

4. Conclusions

This case illustrates the complexity and challenges in the management of ocular infections by rapidly growing mycobacteria, highlighting the need for the development of specific treatment guidelines for these infections.

CRediT authorship contribution statement

David Galindo-Rodríguez: Writing – review & editing, Writing – original draft. **Miguel Moreno Hijazo:** Writing – review & editing, Writing – original draft. **Celina Balint Ilie:** Writing – review & editing. **Daniel Rubio Castro:** Writing – review & editing. **Ignacio Vallés Tormo:** Writing – review & editing. **Eva Gloria Alias Alegre:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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