Review Article

Ocular infections associated with atypical mycobacteria: A review

Shilpa Das, Somasheila I Murthy[1], Tapas Ranjan Padhi[2], Himansu Sekhar Behera[3], Saumya Jakati[4], Savitri Sharma[5], Sujata Das[6]

Atypical mycobacteria or non-tuberculous mycobacteria (NTM) are a group of acid-fast bacteria that are pathogenic to different parts of the eye. The organisms can cause a spectrum of ocular infections including keratitis, scleritis, uveitis, endophthalmitis and orbital cellulitis. Trauma, whether surgical or nonsurgical, has the highest correlation with development of this infection. Common surgeries after which these infections have been reported include laser *in situ* keratomileusis (LASIK) and scleral buckle surgery. The organism is noted to form biofilms with sequestration of the microbe at different inaccessible locations leading to high virulence. Collection of infective ocular material (corneal scraping/necrotic scleral tissue/abscess material/vitreous aspirate, etc.) and laboratory identification of the organism through microbiologic testing are vital for confirming presence of the infection and initiating treatment. In cluster infections, tracing the source of infection in the hospital setting via testing of different in-house samples is equally important to prevent further occurrences. Although the incidence of these infections is low, their presence can cause prolonged disease that may often be resistant to medical therapy alone. In this review, we describe the various types of NTM-ocular infections, their clinical presentation, laboratory diagnosis, management, and outcomes.

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Atypical or non-tuberculous mycobacteria (NTM) are aerobic, non–spore-forming, nonmotile organisms. They are overall a rare cause of ocular infections. Reported first in 1965 by Turner and Stinson as an emerging form of keratitis, there have been several reports of this disease since then.[1] Apart from keratitis, atypical mycobacteria can also cause scleritis and endophthalmitis. An upsurge of atypical mycobacterial infections was noted about two decades ago following laser *in situ* keratomileusis (LASIK).[2] However, since the advent of modern disinfection practices, these have been less frequent. Understanding this disease is important because medical treatment is often prolonged due to delayed diagnosis, inadequate drug penetration, and resistance to antibiotics, leading to increased morbidity and visual loss.[3] In this review article, we focus on the pathogenesis, clinical presentation, and management of atypical mycobacterial ocular infections, highlighting the clinical presentation and management of keratitis, scleritis, and endophthalmitis in separate sections. The terms "atypical" and "non-tuberculous" have been used interchangeably in this article.

Keratitis

Epidemiology and risk factors

Keratitis is the most common ocular infection caused by NTM. The first case of NTM keratitis was reported in 1965.[1] Ever since, these organisms have been identified and reported more effectively. Several species have been reported as a cause of keratitis, such as *Mycobacterium chelonae, Mycobacterium abscessus, Mycobacterium mucogenicum, Mycobacterium szulgai, Mycobacterium fortuitum, Mycobacterium gordonae, Mycobacterium immunogenum, Mycobacterium massiliense,* and *Mycobacterium terrae.* Of these, *M. abscessus, M. chelonae,* and *M. fortuitum* are the most common.[4,5]

Common risk factors for infection include trauma, metallic corneal foreign body, cataract surgery, and refractive surgery, wherein penetration of the corneal epithelium occurs. Contact lens wearers who develop corneal abrasions from extended wear are also at risk.[6] Lin *et al.* investigated 13 cases of NTM keratitis and found that all had history of corneal trauma. There was history of foreign body injury (10), pterygium surgery (two), and penetrating keratoplasty (one).[7] Newman *et al.* reported *M. chelonae* keratitis following trivial surgical trauma during outpatient department (OPD) procedures like suture removal and needle-knife posterior capsulotomy.[8] Neha *et al.* studied 20 patients with culture-positive NTM ocular infections. Majority had keratitis (60%). There was history of trauma in 45% and ocular surgery in 25% of patients.[9]

NTM are known to cause outbreaks of infectious keratitis. This is more common following LASIK surgery.[10,11] NTM keratitis is the most common cause of late-onset infections

Cornea Service, Narayana Nethralaya, Bengaluru, Karnataka, [1]Cornea and Anterior Segment Service, [4]Ophthalmic Pathology Laboratory, [5]Jhaveri Microbiology Centre, L V Prasad Eye Institute, Hyderabad, Telangana, [2]Vitreo Retinal Service, [3]Ocular Microbiology Service, [6]Cornea and Anterior Segment Service, L V Prasad Eye Institute, Bhubaneswar, Odisha, India

Correspondence to: Dr. Sujata Das, Cornea and Anterior Segment Service, L V Prasad Eye Institute, Bhubaneswar, Odisha - 751 024, India. E-mail: sujatadas@lvpei.org

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post-LASIK. NTM-induced post-LASIK keratitis was first reported in 1998.[12] Since then, the reporting has been more frequent, specifically cluster infections. The exact cause for greater association of this pathogen with LASIK surgery has not been established. However, it has been postulated that suboptimal presurgical preparation of patients/multiple uses of microkeratome blades/use of contaminated water and/or inefficient techniques of instrument sterilization may be responsible for the same.[13,14] Intraoperative NTM contamination owing to ice (from tap water) used to chill balanced salt solution (BSS)-filled syringes for intraoperative lavage has been reported post-LASIK.[15] Edens *et al.* reported *M. chelonae* infection associated with humidifier use.[16] Nascimento *et al.* reported 15 eyes with *M. chelonae* infection post-LASIK due to contaminated distilled water.[2] After introduction of femto-second LASIK, there seems to be a decline in the infection rate. Femto-second LASIK uses laser for flap creation (vs. microkeratome blade) and has lesser surgical manipulation, thus resulting in reduced risk of infection.[17-20] The first report of bilateral NTM keratitis after small-incision lenticule extraction (SMILE), successfully managed with medical therapy was reported by Liu *et al.* in 2018.[21]

Srinivas *et al.* reported a cluster of NTM keratitis following penetrating keratoplasty.[22] The first report on nonsurgery-related outbreak of NTM keratitis was published in 2015. This was an occupation-related epidemic of *M. massiliense* keratitis, caused due to release of contaminated aerosols during metal processing by molding machines.[23] NTM keratitis is more common in eyes that have been treated with topical corticosteroids for inflammation associated with trauma/surgery. It has also been reported as interface infection following endokeratoplasty.[24]

Clinical features

The clinical presentation of NTM keratitis is varied and many times indistinguishable from other forms of keratitis. The classic presentation is in the form of "cracked windshield' appearance of the cornea around the edge of a central white ulcer, with radiating lines. However, this is only seen transiently in early stages. This was first described by Lazar *et al.*[25] Other presentations include deep stromal infiltrates, satellite lesions, and dendritic epithelial defects. Lin *et al.*, in their study of 13 cases, described features of NTM keratitis as anterior stromal infiltration (100%), necrotic abscess (69.2%), and migrating lesion (69.2%).[7] In large ulcerations, the organisms can invade the limbus, sclera, anterior chamber, and posterior segment.

Post-LASIK, NTM keratitis presents as interface infiltrates. The organisms gain an access to the interface between the flap and the stromal bed and proliferate within this potential space. In interface keratitis, symptoms appear late due to an intact epithelium and nondense nature of infiltrates initially, unless the visual axis is involved. The infection may present as a single white lesion or multiple granular opacities, along with interface haze.[17,26] Infectious crystalline keratopathy has also been reported.[27] From the LASIK interface, the lesions can spread into posterior stromal bed and anterior corneal flap. Continued progression can result in flap necrosis, perforation, and anterior chamber inflammation progressing to scleritis/vitritis/endophthalmitis.[26] In a patient with NTM keratitis post-SMILE, Liu *et al.* described the presence of multiple white interface infiltrates, progressive and diffuse flap edema, pocket abscesses, anterior chamber exudation, and intrastromal neovascularization bilaterally.[21] Fig. 1 depicts two cases of NTM keratitis.

Treatment and outcomes

Early and accurate microbiologic diagnosis of these infections aids in timely initiation of treatment. If the lesions have a superficial ulceration, it is easy to obtain corneal scraping samples. For stromal and deeper lesions, corneal biopsy is necessary. In LASIK cases, it is important to lift the flap, expose the interface, scrape for microbiologic testing, and simultaneously irrigate with fortified antibiotics before repositing the flap.[20] The American society of cataract and refractive surgery (ASCRS) white paper of 2005 gives recommendations regarding approach to infectious keratitis post-LASIK. While awaiting results of microbiologic testing, it has been recommended that late-onset infections (>2 weeks) be treated with moxifloxacin + fortified amikacin eye drops, thus targeting atypical mycobacteria.[28] Once the result of microbiologic testing is ascertained, the regimen is altered accordingly.

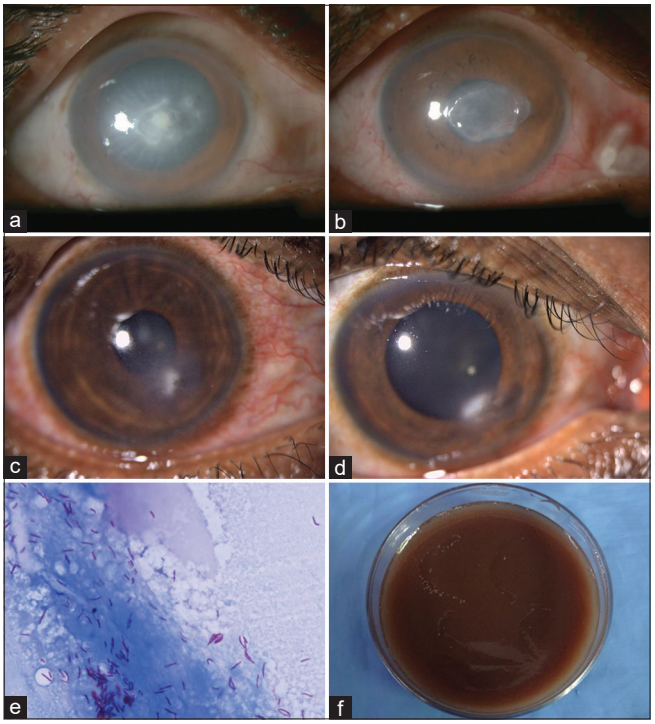

Figure 1: (Case 1) A patient who presented with history of pain, redness, and watering for 1 month duration. (a) At presentation, the patient showed a central epithelial defect with underlying dense, full-thickness corneal infiltrates surrounded by radiating stromal striae, giving a cracked windshield appearance. (b) Microbiologic investigation revealed atypical mycobacteria; the lesion resolved with scarring after 2 months of treatment with fortified vancomycin eye drops. Fortified vancomycin was started as the organism was resistant to other drugs, including amikacin. (Case 2) A 29-year-old man presented with history of pain, redness, watering of right eye of 1-month duration. (c) Slit-lamp picture at presentation showed a small area of infiltrate surrounded by an area of cellularity. (d) Picture after 1 month of starting fortified amikacin drops where the infiltrate started resolving. (e) Corneal scraping specimen stained with Ziehl–Neelsen stain, showing many inflammatory cells and acid-fast bacilli (pink color). (f) Ivory-colored, smooth colonies with elevated centers grown on the blood agar plate

Reports on antibiotic susceptibility testing suggest that the drugs amikacin, azithromycin, and clarithromycin are most effective. Doxycycline, tetracycline, tobramycin, and gentamicin have less *in vitro* activity compared to amikacin. A study to assess minimum inhibitory concentration at which 90% of isolates are inhibited (MIC_{90}) against species *M. fortuitum* and *M. chelonae* showed that fourth-generation fluoroquinolones gatifloxacin and moxifloxacin are effective. A triple-drug regimen consisting of topical amikacin–clarithromycin–moxifloxacin is recommended. Oral clarithromycin, azithromycin, or doxycycline has also been prescribed.[29] Corticosteroids are known to worsen infection. In post-LASIK infections, drug penetration is poor in the interface, hence flap lift/irrigation with antibiotics and, at times, amputating the flap are essential.[30] In case of nonresponse to therapy, penetrating keratoplasty is indicated. Fig. 2 depicts an algorithm for the diagnosis and management of these infections. Table 1 shows the medical and surgical management options for NTM ocular infections, although laboratory antibiotic susceptibility testing is the preferred practice pattern for precisely deciding the drug of choice against these microorganisms.

Management and outcomes of NTM cluster infections post-LASIK, from nine different studies, have been presented in Table 2. Yamaguchi *et al.* studied 39 eyes with post-LASIK

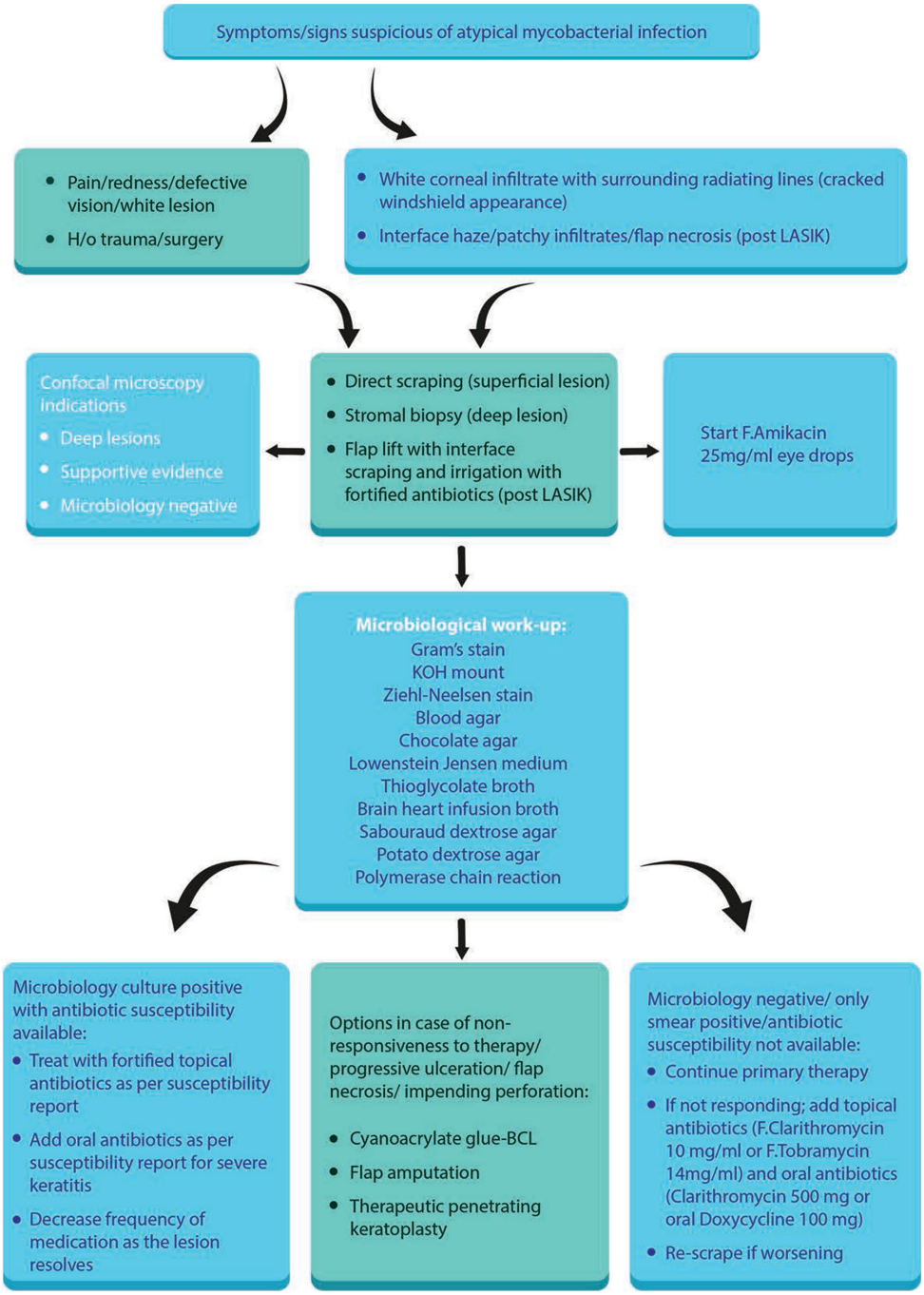

Figure 2: Stepwise algorithmic approach for the diagnosis and management of non-tuberculous mycobacterial keratitis

NTM keratitis; all received topical medication, 28% received oral medication, 56% underwent flap lift/irrigation, and 26% underwent flap amputation. Infection resolved in 1–6 months. Final visual acuity was better than log of minimum angle of resolution (LogMAR) 1.00 in 21 eyes (53.8%).[11] Freitas *et al.* reported 11 cases of post-LASIK NTM keratitis.[10] Patients were treated with topical tobramycin, clarithromycin, and ofloxacin. In severe cases, oral clarithromycin was added. Seven of 11 eyes required flap excision and/or surgical debridement; treatment duration ranged between 2 and 12 months. Final visual acuity varied from Snellen's 20/25 to 20/100.

Of the nine studies on cluster infections (Table 2), drug amikacin was used in six studies as part of medical therapy. With regards to surgical management, flap excision was most commonly performed to aid in resolution of infection. Final vision ranged from snellen's 20/20 to perception of light in these studies.

Scleritis

Epidemiology and risk factors

Atypical mycobacterial scleritis can occur either due to exogenous route of entry of the pathogen (trauma/post surgery) or spread from preexisting keratitis.[31] It is a rarer cause of infectious scleritis, accounting for only 12%.[32] Despite its rarity, it is of significance as its management can be challenging, both due to lack of immune protection to combat infection of the relatively avascular sclera and the poor efficacy of antimicrobials. Previous surgery has the highest association with scleritis.[33] The most common preceding surgeries reported are scleral buckle, pterygium, vitrectomy, glaucoma valves, intravitreal injections, and cataract surgery.[34-39] In an analysis of 18 cases, Kheir *et al.* observed that 94.4% were preceded by surgery, of which 77.8% had undergone scleral bucking.[33] Another predisposing factor is immunocompromised status. Metta *et al.* reported disseminated

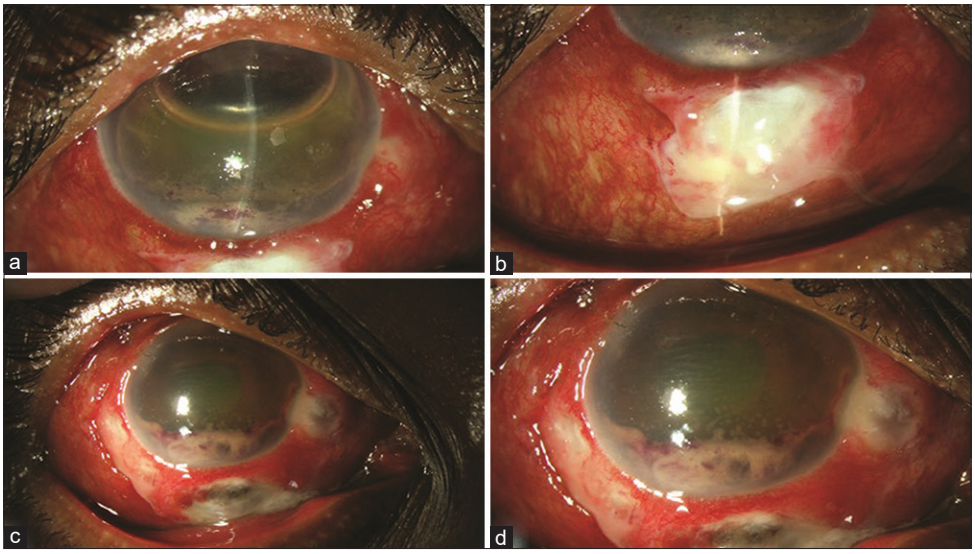

Figure 3: Patient presented with a 6-month history of redness and severe pain, with secondary glaucoma. Examination showed granulomatous uveitis with endothelial exudate and an inferior scleral abscess. (a) The right eye 1 day after scleral biopsy and endo exudates scraping, air bubble and exudation in the anterior chamber, and inferiorly located scleral abscess. (b) The site of scleral involvement is covered with amniotic membrane. (c) Two weeks after starting therapy with fortified vancomycin eye drops; there is not much improvement and dense exudates are noted in the anterior chamber. (d) New lesion is noted nasally

Table 1: Most commonly used medical and surgical management strategies for different NTM infections

NTM infection type	First-line medical management	Second-line medical management (non-responding infection)	First-line surgical management	Second-line surgical management (non-responding infection)
Keratitis	F. amikacin 2.5% e/d + moxifloxacin 0.5% e/d	Add F. clarithromycin 1% e/d + F. tobramycin 1.4% e/d Add oral clarithromycin 500 mg	Debridement and irrigation with amikacin Flap excision (post-LASIK cases)	Cyanoacrylate glue application (cases with perforation) Therapeutic penetrating keratoplasty
Scleritis	F. amikacin 2.5% e/d + moxifloxacin 0.5% e/d Oral clarithromycin 500 mg	Add F. clarithromycin 1% e/d + F. tobramycin 1.4% e/d Add oral doxycycline 100 mg	Debridement and irrigation with amikacin	Scleral patch graft (cases with extreme tissue destruction)
Endophthalmitis	F. amikacin 2.5% e/d + moxifloxacin 0.5% e/d Oral clarithromycin 500 mg	Add F. clarithromycin 1% e/d + F. tobramycin 1.4% e/d Add oral doxycycline 100 mg	Intravitreal amikacin 0.4 mg/0.1 ml injection Intravenous amikacin 500 mg/2 ml	Vitrectomy Removal of intraocular lens-capsular complex and sequestrated exudates Evisceration/enucleation in refractory cases

e/d=Eye drop, F=Fortified, NTM=Nontuberculous mycobacteria

Table 2: Cluster infections associated with atypical mycobacteria

Author, year	Eyes	Risk factor	Infection source	Onset post surgery	Organism	Medical therapy	Surgical therapy	Outcomes/final vision
Chandra *et al.*,[17] 2001	7	LASIK, high dose of topical/oral corticosteroids	Tap water from hospital sink	2–3 weeks	*Mycobacterium chelonae*	Azithromycin, ciprofloxacin, amikacin, clarithromycin, doxycycline	Flap excision (three eyes)	Anterior stromal scarring/ UCVA 20/30 to HM
Holmes *et al.*,[15] 2002	7	LASIK	Ice (from tap water) used to chill BSS	7–24 weeks	*Mycobacterium szulgai*	Ciprofloxacin, amikacin azithromycin, rifampin, clarithromycin, sulfacetamide	Flap excision (one eye)	Corneal scarring (five eyes), clear cornea (two eyes)/UCVA 20/20 to 20/30
Freitas *et al.*,[10] 2003	11	LASIK	Air-conditioner and water from steamer used to clean microkeratomes	3–25 days	*Mycobacterium chelonae*	Tobramycin, clarithromycin, ofloxacin	Flap excision (seven eyes)	Corneal scarring/BCVA 20/25 to 20/100
Winthrop *et al.*,[18] 2003	24	LASIK	Not identified	NA	*Mycobacterium gordonae* (2/24)	NA	NA	NA
Srinivasan *et al.*,[22] 2005	5	PK	Containers for transporting eyeballs	8–24 weeks	*M. chelonae*	Amikacin, gentamycin	Secondary OPK (three eyes)	Corneal scarring (two eyes), graft failure (three eyes)/VA 6/60 to PL
Sampaio *et al.*,[19] 2006	5	LASIK	Not identified	2–3 weeks	*Mycobacterium immunogenum*	Amikacin, clarithromycin, ciprofloxacin	Flap excision (one eye)	NA
Yamaguchi *et al.*,[11] 2011	39	LASIK	Poorly maintained autoclave system	1–52 days	*M. chelonae* (9/39 eyes)	Amikacin, arbekacin, clarithromycin, erythromycin, tobramycin, moxifloxacin, gatifloxacin	Flap excision (10 eyes), secondary OPK (five eyes)	Corneal scarring/BCVA 1.20 decimals to HM
Hung *et al.*,[23] 2016	3	Occupation related	Aerosols generated during metal processing by molding machines	NR	*Mycobacterium massiliense*	Amikacin, moxifloxacin, levofloxacin, azithromycin	None	Corneal scarring/VA 20/20 to 20/400
Nascimento *et al.*,[2] 2018	15	LASIK	Distilled water from storage tank and portable steamer reservoir	9–20 days	*M. chelonae* (7/15 eyes)	Clarithromycin, tobramycin, gatifloxacin	Flap excision (eight eyes)	Corneal scarring/BCVA 20/20 to 20/30

BCVA=Best corrected visual acuity, BSS=Balanced salt solution, HM=Hand motions, LASIK=Laser *in situ* keratomileusis, NA=Not available, NR=Not relevant, OPK=Optical penetrating keratoplasty, PK=Penetrating keratoplasty, PL=Perceptions of light, PR=Perceptions of rays, UCVA=Uncorrected visual acuity, VA=Visual acuity

M. chelonae infection with spondylodiscitis, spinal epidural abscess, and scleritis in a patient on interleukin-2 therapy for medullary hypoplasia.[40] Some cases have been reported to occur *de novo*, with no obvious predisposition.

Clinical features

Delayed and insidious presentations are a hallmark of this infection. In those cases, following scleral buckling, the infections presented after several days to months of the surgery, with a range of 1.5–40 weeks.[33] In the initial stage, the infection can resemble immune-mediated disease. Some of these patients may already be on oral corticosteroids. Prominent and characteristic features of this infection are conjunctival and scleral abscesses [Fig. 3].

In case of buckle infections, exposure of scleral buckle, scleral erosion, and discharge may be noted. In other cases, nodules are noted at the surgical sites (pterygium excision and glaucoma implant surgery) and suture abscesses after vitrectomy at the site of scleral port.[36-38] Cases with *de novo* presentation have been reported as isolated scleral nodules. Pisitpayat *et al.* reported two cases of *Mycobacterium haemophilum* infection, of which the first was in an immunocompromised individual and presented with multiple pustular lesions.[41] The second case presented with nodular scleritis with keratouveitis and radial keratitis.

Treatment and outcomes

It is recommended in all cases of infectious scleritis to obtain scrapings from the nodules and/or biopsy of the affected site. The specimens should be subjected to microbiology and histopathology [Fig. 3]. Explanted scleral buckles should also be subjected to microbiology. Management and final visual outcome are often confounded by delayed diagnosis.

Topical amikacin eye drops (2.5%) every hour and oral rifampicin/clarithromycin or doxycycline is the preferred treatment. The *in vivo* efficacy of the drugs may be poorer than the *in vitro* sensitivity; thus, combination therapy is advocated, which may include topical ciprofloxacin/moxifloxacin/azithromycin as well. These infections often tend to recur after cessation of therapy; therefore, therapy with at least two drugs and prolonging treatment for 4 weeks to 6-months (in some cases) after the resolution of clinical signs is recommended. Topical corticosteroids are best avoided.[5] In cases with multiple scleral abscesses, surgical debridement is recommended. Local injection or irrigation with amikacin can also be performed intraoperatively. Removal of the infected buckle/other contaminated material and debridement are necessary in most cases. In cases with extreme tissue destruction, scleral patch grafts may be necessary. Table 1 shows the medical and surgical management options for NTM infections, although laboratory antibiotic susceptibility testing is the preferred practice pattern for precisely deciding the drug of choice against these microorganisms. Complete resolution of infection can be expected in most cases if timely microbiologic diagnosis is made. Kheir *et al.* reported suboptimal visual outcomes, with 71.4% eyes achieving visual acuity of ≤20/200 (Snellen's) despite achieving resolution of infection in 94.1% cases (16/17 eyes).[33]

Endophthalmitis

Epidemiology and risk factors

Endophthalmitis caused by NTM is a rare but serious intraocular infection posing diagnostic and management challenges. Common agents incriminated so far include *M. fortuitum*, *M. chelonae*, *M. haemophilum*, *M. goodii*, *M. avium-intracellulare*, *M. gordonae*, *M. abscessus*, *M. triplex*, *M. marinum*, *M. sulzi*, *M. flavescence,* and *M. xenophi*.[42,43] Since its first report in 1973, endophthalmitis due to NTM has been increasingly reported because of awareness about this possibility, increase in immunocompromised hosts, and improved microbiologic testing.[44]

Most often, the infection has been reported to follow cataract surgery, penetrating keratoplasty, glaucoma-filtering surgeries/drainage devices, scleral buckles, suture infiltrates, and corneal ulcers.[5] The implants often act as a nidus for biofilm deposition by NTM, which in turn acts as a barrier against effective penetration of antibiotics leading to persistent infection. Sometimes, these organisms get sequestered in clusters behind an intraocular lens or within the capsular bag as a plaque.[45] Endogenous endophthalmitis due to NTM is more common in immunocompromised states like acquired immunodeficiency syndrome (AIDS), malignancy, uncontrolled diabetes, kidney transplantation, and prolonged use of corticosteroids/immunosuppressive drugs.[46]

Clinical features

The presentation is typically a chronic recurrent or persistent intraocular inflammation often resistant to topical corticosteroids. Sometimes, the infection can have an acute presentation. Majority are exogenous infections. Diagnosis of atypical mycobacterial endophthalmitis is often delayed. An awareness of such a possibility, high index of suspicion, and a search (clinical and microbiological) targeted at detection of these organisms are crucial for early diagnosis. Any low-grade prolonged intraocular inflammation often with recurrence in the setting of previous intraocular surgeries, plaque on IOL surface/anterior hyaloid, intracapsular precipitate, immunocompromised status, and/or poor response to topical corticosteroids is suggestive of this infection.[6]

Treatment and outcomes

Eary initiation of medical therapy and early vitrectomy with a targeted microbiologic analysis is crucial for a successful outcome. Drugs, namely, amikacin, clarithromycin, and azithromycin, have been reported to be the best.[6,43] There is a report of endophthalmitis by *M. abscessus* in an oil-filled eye that responded well to intravitreal piperacillin and tazobactam.[47] Nonresponding or recurrent cases benefit from aggressive surgical debridement like repeat vitrectomy, removal of intraocular lens–capsular complexes, and/or removal of sequestrated exudates/abscesses including those on the posterior iris surface and ciliary body.[48] Table 1 shows the medical and surgical management options for NTM infections, although laboratory antibiotic susceptibility testing is the preferred practice pattern for precisely deciding the drug of choice against these microorganisms.

Periods of quiescence are common with endophthalmitis of this type, and it is important not to mistake the stage of quiescence as cure, but be vigilant with a close watch for any recurrence. NTM endophthalmitis usually has a poor visual outcome. Difficulty and delay in the initial diagnosis, ability to form biofilms, sequestration at different inaccessible locations, and resistance to conventional intravitreal agents are the reasons for high virulence and poor visual outcomes. Evisceration/enucleation is indicated in refractory cases.[49]

Laboratory Diagnosis

Laboratory diagnosis of atypical mycobacterial ocular infections is often challenging due to low index of clinical suspicion, prolonged use of topical corticosteroids and antibiotics, its slow-growing nature, and its complex cell wall composition. Laboratory diagnosis is mainly achieved by immediate microscopic examination followed by culture of clinical samples. Addition of advanced molecular diagnostics such as polymerase chain reaction (PCR) in routine diagnostic testing has increased the sensitivity, specificity, and rapidity of diagnosis significantly.

Sample collection

As for any other infection, samples for the diagnosis of NTM infections must be collected from the site of infection following sterile procedures. Smears are prepared on slides by rubbing the material on to a 1-cm area in the center. The culture media are either inoculated directly with the sample in the clinic or in the laminar flow hood at the laboratory.

Since NTM have been reported to cause a variety of ocular infections, different types of samples are collected based on the infection site. The clinical specimen collected from orbital infections includes purulent discharge, drainage of abscesses, and/or orbital tissues. In case of eyelid/periocular skin infections, purulent discharge is collected with a swab, whereas material from incision drainage/biopsy of nodular lesions is collected and inoculated on culture media directly. In ulcerative keratitis cases, superficial corneal scraping is collected. In case of deep-seated stromal infiltrates, corneal biopsy increases the sensitivity of diagnosis. In scleritis cases, scleral biopsies of abscesses and nodules are collected. In cases of endophthalmitis, the aqueous humor or vitreous fluid is collected. Tissue samples for molecular diagnosis are collected in 200-µl phosphate buffer saline, which can be stored at 4°C till further processing. Fluid samples such as anterior chamber (AC) fluid and vitreous can be collected in dry tubes and submitted to the laboratory directly. If a delay of over 24 h is anticipated, the samples should be kept at – 20°C till further processing.[50]

Processing of clinical samples

Since the samples collected from ocular infections are scanty, they require special care while processing and inoculating into different culture media. Direct patient side smear preparation and inoculation in different culture media increases the sensitivity of diagnosis. Purulent discharge, drainage of abscesses, superficial corneal scraping, vitreous fluid, and aqueous humor can be directly processed for smear examination and culture. Samples such as corneal buttons, biopsies, and eviscerated contents can be collected in sterile Petri plates. Such samples can be aseptically cut into many fragments (under laminar flow hood) before inoculating into different culture media. Smears cannot be made from certain samples such as corneal buttons, contact lenses, intraocular lenses, corneal biopsy, and iris tissue. Hence, culture is the only option for definitive diagnosis of such samples.[50] For molecular diagnosis, DNA should be extracted from clinical samples using either manual procedures or available commercial DNA isolation kits.

Microscopic evaluation

Direct microscopic examination of smear is the most rapid and reliable method of diagnosis that guides an early initiation of antibiotics. Gram stain is the basic stain that gives a clue about the organism. Presence of gram-positive, partially stained, beaded bacilli (ghost cells) is suggestive of atypical mycobacteria.[51] Zeihl–Neelsen stain with 20% H_2SO_4 is used for definitive diagnosis, in which the organisms appear as slender, acid-fast, pink-beaded bacilli.

Culture

Inoculated culture media are incubated at 37°C in aerobic conditions. Atypical mycobacteria are slow-growing and fastidious organisms. They can grow in media such as blood agar/chocolate agar as well as special media such as lowenstein-jensen (LJ) media. Colony morphology may vary from species to species; it may be smooth/rough and pigmented/nonpigmented. Growth of mycobacteria is stimulated by CO_2 and fatty acids. Optimum temperature varies from 30°C to 45°C, with a high generation time (20 h).

All culture media need to be examined regularly to find the presence of any relevant colony. If any smooth/rough and pigmented/nonpigmented, dry-looking colonies appear on the streaking marks over blood agar or chocolate agar plates, they are further gram stained to visualize the morphology. If turbidity appears in liquid culture media, then it needs further subculture in either blood agar or chocolate agar and gram's staining.

Identification

Mycobacteria are preliminarily identified by traits such as growth rate, temperature required for growth, and pigmentation of colonies. These features direct the selection of key biochemical tests to further characterize them. Detailed descriptions of methods of biochemical testing can be obtained from several sources.[52] High-pressure liquid chromatography of mycolic acid esters has been demonstrated to be a rapid method for identification of some *Mycobacterium* species.[53] Genotypic identification has become a reality with the availability of genome sequences of large number of mycobacteria. Genomic sequence information has facilitated identification through different molecular techniques like PCR and restriction endonuclease analysis,[54,55] acridinium ester-labeled DNA probe-based detection of rRNA,[56] INNO-LiPA tests,[57] and DNA sequencing.[9,58] Relevant molecular typing methods include restriction fragment length polymorphism using molecular markers and pulsed-field gel electrophoresis.[13]

Antibiotic susceptibility

Antimicrobial susceptibility testing is equally important as that of identification, for suggesting an appropriate antibiotic therapy.[5,59] Three methods have been described for *in vitro* susceptibility testing of NTM: broth microdilution, disk diffusion, and E test.[59,60] Majority of reports suggest that drugs amikacin and clarithromycin are most active against NTM.[61,62] Citron and Hecht described antimicrobial agents, range of test concentration, and criteria for interpretation.[63] Breakpoints for interpretation are available for limited number of antimicrobial agents. Testing 112 ocular isolates, Brown-Elliot *et al.*[64] found amikacin, clarithromycin, and tobramycin to be the most effective. Tobramycin was 8-fold more active than amikacin for *M. chelonae* and had equivalent activity for *M. abscessus*. Girgis *et al.* found that most NTM isolates were sensitive to clarithromycin (93.2%) and amikacin (81.3%).[4] Neha *et al.* recently reported the testing of 20 isolates of NTM by disk diffusion method and found highest susceptibility for amikacin (75%). The susceptibility to moxifloxacin/

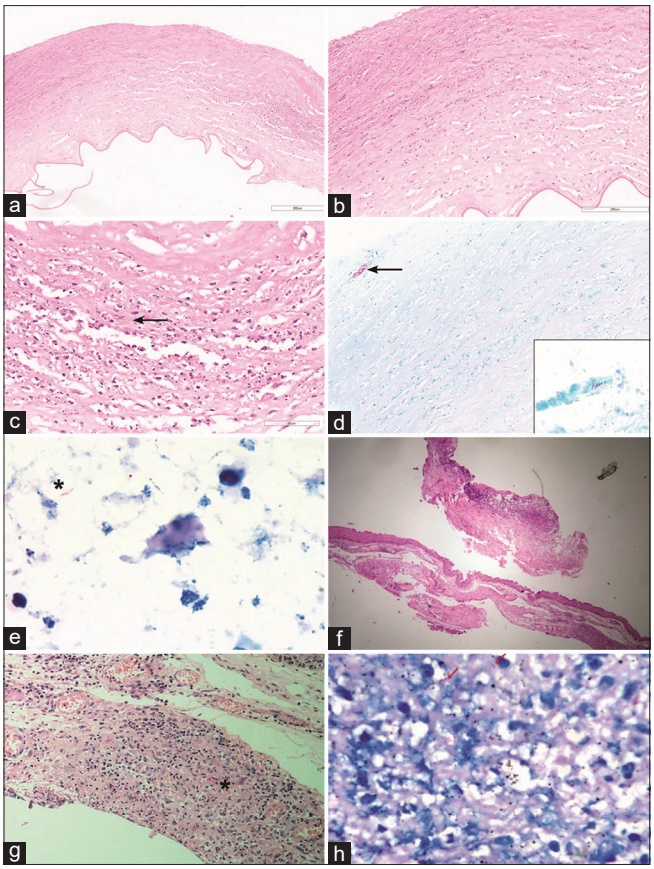

Figure 4: Histopathology of atypical mycobacterial keratitis showing (a) loss of lamellar architecture (H and E, 8× original magnification); (b) ulcerated epithelium, destroyed Bowman's membrane, and diffuse stromal infiltrates (H and E, 15× original magnification); (c) stromal infiltrates composed of lymphocytes, neutrophils, and plasma cells with ill-defined granuloma (arrow) (H and E, 40× original magnification). (d) Ulcer bed shows slender, beaded 20% acid-fast bacilli (inset) (Ziehl–Neelsen, 100× original magnification). Microbiology and histopathology of scleritis: (e) photomicrograph of smear from scleral scrapings shows scattered epithelial cells along with debris and thin, slender, and beaded bacilli (asterisk), which appear bright pink on Ziehl–Neelsen staining (100× original magnification); (f) scanner view of the scleral biopsy shows intact epithelium and underlying substantia propria with dense inflammatory infiltrates (H and E, 4× original magnification); (g) higher magnification image of aggregates of epithelioid cells forming granuloma (asterisk) admixed with neutrophils and blood vessels (H and E, 40× original magnification); (h) thin, slender, beaded acid-fast bacilli (red arrows) are noted in clusters and are also singly scattered (Ziehl–Neelsen, 100× original magnification). H and E = hematoxylin and eosin

ciprofloxacin, cefotaxime, and tobramycin was 35% each.[9] Most of the strains were resistant to cefazolin, chloramphenicol, gatifloxacin, gentamicin, and ceftazidime. Reddy *et al.* applied the E test method for susceptibility testing of NTM organisms from corneal scrapings. They concluded that topical amikacin in combination with oral clarithromycin/azithromycin is the best option for management of rapidly growing NTM keratitis.[65]

Histopathology

Biopsied or debrided infectious ocular tissues can also be submitted for histopathology to study the histologic changes and aid identification of these organisms, especially in microbiology-negative cases. Based on cell-mediated/humoral immunity status of the patient, the tissue histologic features are varied, ranging from chronic nonspecific inflammation to granulomatous inflammation characterized by aggregates of epithelioid cells forming granulomas with or without central caseous necrosis and fibrosis.[66] The density of the organisms is more in immunocompromised cases. Fluorescent auramine O stain can be used to highlight atypical mycobacteria.

Keratitis

Corneal specimens frequently show epithelial ulceration with chronic inflammatory infiltrates in the stroma. There are reports of dense polymorphonuclear inflammatory reaction with microabscess formation. Occasionally, chronic inflammatory response can be seen. Karp *et al.* reported that NTM are usually noted in the interlamellar stromal clefts as shown in Fig. 4a–d.[67]

Conjunctivitis and scleritis

Involvement of conjunctiva is relatively uncommon. Chronic granulomatous inflammation with microabscess formation and aggregates of the acid-fast bacilli may be seen in such cases. Scleral biopsies of nodules/abscesses/vitrectomy ports have shown features of chronic granulomatous inflammation [Fig. 4e–h].[37] Severe inflammation and necrosis may result in perforation of the globe.

Uveitis and endophthalmitis

Diagnosis is primarily based on cytology smears or cell block preparation of vitreous.[33] Cases with human immunodeficiency virus (HIV) infection have shown extensive choroidal involvement with severe granulomatous reaction. Nodule formation composed of epithelioid cells/histiocytes showing granulomatous inflammation has been reported.[44,68]

Orbit and eyelid infections

Orbital tissues show varied histomorphologic features in cellulitis cases like chronic inflammation with noncaseating granulomas, florid necrotizing cellulitis with infarction,[69] and lipogranulomatous inflammation.[70] Erythematous eyelid or lacrimal nodules when biopsied also show similar features of chronic granulomatous inflammation and necrosis.

Conclusions

Atypical mycobacteria cause a wide range of infections of the eye. They pose a challenge for treatment due to indolent clinical course and poor response to treatment. Recent development in laboratory techniques has improved diagnosis. Combination therapy has better prognosis compared to monotherapy. Future research needs to focus on rapid diagnostic tests to determine antibiotic susceptibility and better treatment measures.

Literature Search

Review of articles was carried out from the databases "PubMed" and "Google Scholar" published (up to year 2021) on "Ocular infection due to atypical or non-tuberculous mycobacteria». Keywords used- "Atypical Mycobacteria," "Non-tuberculous Mycobacteria," "Keratitis," "Scleritis," "Endophthalmitis," "Microbiology," and "Pathology."

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