Non-tuberculous mycobacterial keratitis

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Abstract

Non-tuberculous mycobacteria are environmental, opportunistic pathogens that are increasingly being recognized as important causes of many human diseases. Among them, rapidly growing mycobacteria are the most notorious organisms causing infectious keratitis. Non-tuberculous mycobacterial (NTM) keratitis commonly occurs after trauma or refractive surgery, and can masquerade as fungal, herpetic or amoebic keratitis. Therefore, the diagnosis is often delayed. Prolonged medical treatment and judicious surgical debridement are required in order to eradicate the pathogens. Combination therapy with aminoglycosides, macrolides and fluoroquinolones improves the prognosis and decreases the occurrence of drug resistance. However, regardless of the development of new diagnostic techniques and antimicrobials, NTM keratitis remains a clinical challenge for most ophthalmologists. In this article, we provide a concise introduction to the epidemiological features and clinical characteristics of NTM keratitis, and the modern diagnostic tools used for it. We also summarize the current concepts of prevention and treatment for this potentially devastating condition.

Keywords: Atypical mycobacteria, infectious keratitis, microbial keratitis, non-tuberculous mycobacteria, ocular infection

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Introduction

Since the first report published by Turner in 1965 [1], non-tuberculous mycobacteria have become increasingly recognized as important causes of infectious keratitis [2–5]. Traditionally, non-tuberculous mycobacteria have been divided into Runyon groups I–IV on the basis of colony characteristics [6]. Runyon group IV, known as the rapidly growing mycobacteria (RGM), is the most noticeable group of human keratitis pathogens [1,4,5,7]. Of all reported cases of non-tuberculous mycobacterial (NTM) keratitis, 83.5% are caused by two subgroups of RGM, the Mycobacterium fortuitum group and the Mycobacterium chelonae–abscessus group [5]; the other 16.5% of cases are caused by Runyon groups I–III, the slowly growing mycobacteria (SGM) or non-tuberculous mycobacteria of unknown species. The SGM, Mycobacterium szulgai, Mycobacterium terrae, Mycobacterium gordonae, Mycobacterium marinum, Mycobacterium avium–intracellulare, Mycobacterium nonchromogenicum, Mycobacterium triviale and Mycobacterium asiaticum have been reported to infect the human cornea [5].

Unlike for tuberculosis and leprosy, the environment is considered to be the source of human NTM diseases. Non-tuberculous mycobacteria are present in natural waters and soils worldwide [8,9]. An important pathogenic property of non-tuberculous mycobacteria is in their ability to develop biofilm. Biofilm protects non-tuberculous mycobacteria from disinfectants, and facilitates their attachment to the surface interface. As a result, non-tuberculous mycobacteria can also survive in artificial environments, such as daily water distribution systems in operating theatres and swimming pools [10]. The biofilm then contributes to the opportunistic NTM infection. We have reviewed the risk factors for the development of NTM keratitis, the epidemiology, and the clinical presentation. Current trends in diagnosis and treatment have also been emphasized, followed by an analysis of general outcomes.

Risk factors

An important risk factor for the development of NTM keratitis is trauma with penetration of the corneal epithelium [5]. The
epithelium is the first barrier for most pathogens. Therefore, contact lens wearers who develop corneal abrasions appear to be at risk of NTM infection [11]. Trauma, including that caused by corneal foreign bodies [2], ocular surgery [12], and trivial procedures such as suture removal [13], can all inoculate the non-tuberculous mycobacteria into the deep corneal stroma. Patients receiving topical steroids, such as corneal transplant recipients, are also at risk [12]. Steroid use will suppress the granulomatous inflammation and facilitate the growth of non-tuberculous mycobacteria [14].

After the mid-1990s, with the advances in refractive surgery, the number of cases of NTM keratitis after laser-assisted in situ keratomileusis (LASIK) increased dramatically [4,5,7]. Outbreaks of NTM keratitis after LASIK have been reported in Brazil, the USA, and Japan. These outbreaks were related to improper sterilization of surgical fluid and instruments [15–17], leading to the pathogens being introduced into the corneal stroma during a surgical procedure.

Epidemiology

The overall incidence of infectious keratitis ranges between 0.0063% and 0.71%, with higher rates in developing countries [18]. Regional variations in causative organisms do exist. The data taken from two large referral centres have shown that non-tuberculous mycobacteria are identified in only 1.1–7.9% of all cases of infectious keratitis [3,19]. Although the overall incidence of infectious keratitis after LASIK is still low, with an incidence between 0.035% and 0.31% in recent reports [20], non-tuberculous mycobacteria have been reported to be some of the most common pathogens (47%) causing post-LASIK keratitis [21].

The cases of NTM keratitis can be divided into two main groups, i.e. post-LASIK and non-LASIK-related groups. The age of patients developing NTM keratitis post-LASIK ranges between 23 and 57 years, with a mean age of 37 years, reflecting the younger population receiving refractive surgery [21]. Men and women are equally affected. Right eyes are more commonly infected than left eyes, because the right eye is usually treated first in a simultaneous bilateral procedure, and thus receives more inocula. Ten percent of the post-LASIK NTM keratitis patients have bilateral diseases [4,5]. Among the group of non-LASIK-related NTM keratitis, the most common cause is ocular trauma. The mean age ranges between 47 and 61 years. Men are predominantly affected (up to 70%), owing to a higher prevalence of trauma in males [2,3,22]. No bilateral cases of non-LASIK-related NTM keratitis have been reported, and no laterality has been observed [5].

Clinical features

Patients with NTM keratitis often have a history of trauma with corneal foreign bodies or ocular surgery. The patients usually complain of decreased vision, photophobia, and a variable degree of pain [2,3]. The symptoms are caused by a defect in the corneal epithelium, with inflammation of the underlying corneal stroma caused by replicating organisms [18]. The presentation of post-LASIK NTM keratitis is usually more indolent than that of cases caused by trauma [5]. The time interval between the onset of trauma and the appearance of corneal infection ranges from days to weeks, whereas the average time between LASIK and the onset of NTM keratitis is 3.4 weeks, and is up to 10–14 weeks in cases of keratitis caused by SGM after LASIK [4].

The clinical manifestations of corneal lesions are variable. The corneal infiltrates may be multifocal, or there may be a single main lesion surrounded by many white, satellite lesions [2,14,23]. Up to one-third of NTM keratitis cases may have no epithelial defect at initial presentation [3]. This finding suggests that the infectious process is slow, and that the corneal epithelium can heal after the infiltrate extends to the corneal stroma. This is contrast to the typical findings of epithelial

FIG. 1. Characteristic patterns of non-tuberculous mycobacterial keratitis. (a) Mycobacterium fortuitum keratitis showing paracentral stromal infiltrates with radiating projections, mimicking a ‘cracked windshield’ appearance. (b) Infectious crystalline keratopathy characterized by white, crystalline, refractile, branching stromal infiltrates.
Acanthamoeba can mimic those of infectious keratitis from other causes, duration has shortened. The clinical features of NTM keratitis [2,3]. However, as clinicians have gained more experience, the onset to diagnosis is 10 weeks (range: 1 week to 2 months) [23]. Studies have shown that the average duration from symptom to diagnosis is 10 weeks (range: 1 week to 2 months) [23]. The diagnosis of NTM keratitis is often delayed [2,3,5]. Earlier diagnosis can be observed in NTM keratitis patients after either trauma or LASIK. In general, patients with a history of minor corneal trauma, such as corneal abrasion or that caused by a foreign body, may present with a superficial process and less inflammation; whereas patients with a history of intraocular surgery, such as penetrating keratoplasty or cataract extraction, tend to develop deeper and denser infiltrates of the wound [2]. For post-LASIK patients, the lesions appear to be entirely within the lamellar flap or at the flap interface. Anterior extension of infiltrates with flap perforation or posterior extension into the stroma is less frequent, and occurs in cases with delay treatment [4,5,21].

**Diagnosis**

The diagnosis of NTM keratitis is often delayed [2,3,5]. Earlier studies have shown that the average duration from symptom onset to diagnosis is 10 weeks (range: 1 week to 2 months) [2,3]. However, as clinicians have gained more experience, the duration has shortened. The clinical features of NTM keratitis can mimic those of infectious keratitis from other causes, especially fungus, herpes simplex virus, and *Acanthamoeba* [5,7]. All of these cases may be associated with a history of ocular trauma, and present with corneal infiltrates with an intact epithelium, a waxing and waning course, and a poor response to antibiotic treatment. The definite identification of the causative organism requires corneal scraping to obtain materials for stains and cultures. For cases of keratitis after LASIK, the flap should be lifted, and cultures from the interface should be performed [21].

Acid-fast stains, such as Ziehl–Neelsen stain, are commonly used in modern laboratories [5,8]. It is important to mention that an inadequate amount of specimen and the difficulty in decolorizing non-tuberculous mycobacteria at 20% sulphuric acid lower the accuracy of diagnosis. Acid-fast stain has a sensitivity of only 22–78% as compared with culture [25]. Fluorescein-conjugated acid-fast stains can be helpful in increasing the detection rate [26].

Although the exact sensitivities and specificities of the culture techniques are not yet well established, the importance of culturing the infected tissues cannot be overemphasized [27]. Cultures amplify the scant amount of organisms available in keratitis patients. In addition, cultures allow both pathogen identification and antibiotic susceptibility testing. All cultures for suspected NTM cases should be performed on solid and broth media. The advantages of solid media are numerous [28]. They allow the observation of colony morphology and growth rates, recognition of mixed infections, and quantification of the infecting organisms. The simultaneous use of multiple culture media, including Löwenstein–Jensen medium, blood agar, MacConkey agar, and Middlebrook 7H10 and 7H11 media, increases the growth of pathogens, and aids in the identification of specific non-tuberculous mycobacteria, particularly the slow growers [5,8,27].

Culture time may be relatively short (within 1 week) if RGM are present, but the cultures should be kept for up to 8 weeks to ensure the growth of slow growers [5,8,27]. If an inadequate quantity of specimen is collected, small amounts of specimen can be mixed with sterile, balanced saline solution and sent for culture in broth media, such as modified Middlebrook 7H9 in conjunction with a fluorescent mycobacterial growth indicator [5,8,27].

Categorizing the non-tuberculous mycobacteria to the species level can provide correct characterization and information for antibiotic selection [8]. Studies have shown that molecular phenotyping of non-tuberculous mycobacteria with PCR-based technology is more rapid and specific comparing to traditional growth and biochemical tests [28]. For example, PCR restriction fragment length polymorphism analysis has been used to identify a case of *M. szulgai* keratitis [29]. In addition, primers targeting the heat shock protein 65 (*hsp65*) region of the mycobacterial genome have been used to identify *M. abscessus* and *M. fortuitum* in patients with postoperative endophthalmitis [30].

**Medical Treatment**

Medical treatment of NTM keratitis is often unsatisfactory, because of delayed diagnosis, inadequate drug penetration, and slow response to therapy. Resistance to most conventional antibiotics and the emergence of resistant strains during long-term treatment also contribute to poor therapeutic results [4,5,31]. As the antibiotic susceptibility of NTM isolates varies among different species, an in vitro susceptibility test of each individual strain is the cornerstone for antimicrobial selection [5,8,27]. The broth microdilution test is the reference technique for testing the antimicrobial susceptibility of non-tuberculous mycobacteria [8]. However, this method can be difficult to perform for many laboratories.
in daily practice, owing to difficulties in microtitre plate preparation and in reading the results. Other methods, such as the disk diffusion assay [32] and the Etest assay [33], have also been evaluated; however, the results are less consistent than those obtained with the broth microdilution method [8].

Aminoglycosides, macrolides and fluoroquinolones are the drugs that non-tuberculous mycobacteria are considered to be sensitive to [5,23]. Earlier reports focusing on in vitro susceptibilities have suggested that aminoglycosides, especially amikacin, are the drugs of choice for NTM keratitis [34]. Furthermore, therapeutic levels of aminoglycosides can be achieved by hourly application of fortified amikacin in rabbit corneas [35]. However, its clinical result remains unsatisfactory [2]. With single-agent therapy, it has been reported that the failure rate can reach up to 60% in patients. In addition, highly concentrated topical amikacin is poorly tolerated. Conjunctival injection, chemosis and necrosis have been observed clinically [36]. As a result, long-term use of topical amikacin leads to poor compliance.

Macrolides, especially clarithromycin, have been shown to have good in vitro sensitivity and favourable corneal penetration [37,38]. Although macrolides are considered to be bacteriostatic, clarithromycin may provide a bactericidal effect if used at a high concentration [37]. Even though the in vitro efficacy of clarithromycin against non-tuberculous mycobacteria is not as good as the in vitro data would suggest [39], treatment with topical clarithromycin or systemic clarithromycin has been reported to be successful for NTM keratitis [3,5]. However, toxic reactions and drug intolerance with frequent topical clarithromycin application should also be monitored [3].

Quinolones, such as ciprofloxacin, gatifloxacin, and moxifloxacin, have all been reported to be effective topical agents for NTM keratitis [40,41]. The in vitro susceptibility of non-tuberculous mycobacteria to fluoroquinolones varies from resistant to sensitive among different studies [41,42]. An animal study showed that ciprofloxacin had similar efficacy to amikacin and clarithromycin for M. chelonae keratitis [39]. Topical ciprofloxacin has been used to treat patients with NTM keratitis who did not response to amikacin therapy. However, the response rate with ciprofloxacin treatment is only 44% [43]. Generally, fluoroquinolones have better activity against M. fortuitum than against M. chelonae–abscessus [8,25,43]. The fourth-generation fluoroquinolones, including gatifloxacin and moxifloxacin, have a methyl group at C8. This structural modification contributes to their superior bactericidal activity and better ocular penetration than those obtained with older generations of fluoroquinolones [44]. As a result, fourth-generation fluoroquinolones have been reported to give more favourable clinical outcomes, and are considered to be alternative treatments for NTM keratitis [5,40].

NTM keratitis is clinically recalcitrant to treatment, and requires long-term therapy to eradicate infection [3,5]. There are no clear guidelines for the duration of therapy. The average duration of treatment ranges from weeks to months [5]. Acquired resistance to amikacin, clarithromycin and fluoroquinolones restricts the use of these agents as monotherapy [45]. Although in vitro studies have demonstrated that amikacin combined with a fluoroquinolone or clarithromycin shows no synergistic effect [32,46], combination therapy with two or more antimicrobial agents is still recommended to decrease the risk of the development of drug resistance [5]. Triple therapy with amikacin (50 mg/L), topical clarithromycin (10 mg/L) and fourth-generation fluoroquinolones is suggested for NTM keratitis [5]. Systemic antibiotics, such as clarithromycin and doxycycline, may also be used for recalcitrant cases. Another important concept in the management of NTM keratitis is the avoidance of topical steroids. Corticosteroid therapy may reduce the local host immune defence and contribute to the development or progression of NTM keratitis [3].

**Surgical Treatment**

The treatment of NTM keratitis requires not only appropriate antibiotic therapy but also judicious surgical debridement [2,5,31]. Progression or lack of response to topical therapy should, in most cases, be followed by surgical interventions. As most cases of NTM keratitis are localized to the superficial stroma, lamellar keratectomy is advocated for the treatment of NTM keratitis. Lamellar keratectomy for removal of the infiltrated corneal stroma offers several beneficial effects, lowering the bacterial load, facilitating antibiotic penetration, removing the necrotic corneal stroma to facilitate re-epithelialization, and providing sufficient tissue for culture and histopathological diagnosis [31]. In cases of post-LASIK NTM keratitis, immediate flap lifting, scraping and irrigation of the stromal bed with fortified antibiotics are recommended. Flap amputation is commonly performed in recalcitrant and deeply seated infections [7,21]. Penetrating keratoplasty or deep anterior lamellar keratoplasty is usually reserved for intractable NTM keratitis [47]. All surgical procedures have the risk of recurrence if adequate margins are not obtained, requiring additional surgical procedures. In advanced cases of NTM keratitis, the infection can progress to the corneoscleral junction and lead to endophthalmitis. Aggressive surgical debridement with pars plans vitrectomy, intravitreal antibiotic injection or even enucleation may be
necessary to eradicate the infection and to prevent systemic involvement [18].

Outcomes

The prognosis for NTM keratitis remains unsatisfactory [5]. Earlier studies comparing the outcomes of different types of infectious keratitis have shown that NTM keratitis has the poorest response to medical treatment. Of patients suffering from NTM keratitis, 68–85% require surgical intervention [2,3,18]. The use of topical clarithromycin, amikacin and newer-generation fluoroquinolones has improved the general outcomes in the last two decades [4,5,7]. Clinicians today have a higher degree of suspicion regarding non-tuberculous mycobacteria as a common cause of post-trauma or post-LASIK keratitis. Therefore, we can recognize the infection earlier and prompt rapid medical or surgical treatment. According to the survey by Chang et al. in 2004 [21], 50% of post-LASIK NTM keratitis patients were reported to have moderate vision loss, whereas in a recent outbreak of post-LASIK NTM keratitis that occurred between 2008 and 2009 in Japan, only 17.9% of patients had final visual acuity worse than 20/40 [48].

Conclusions

Non-tuberculous mycobacteria, especially the RGM, have been continuing to emerge as important human pathogens that cause infectious keratitis. These opportunistic pathogens can form biofilm and survive in artificial environments. Recommendations for outbreak prevention include rigorous instrument sterilization and the avoidance of possible contamination of the surgical field with tap water or distilled water. Clinicians should have a high index of suspicion for recalcitrant inflammation processes following trauma and LASIK. Adequate sampling for laboratory tests is important for early diagnosis and susceptibility testing. The avoidance of steroid treatment, and the use of combination therapy with topical or systemic amikacin, clarithromycin and fluoroquinolones, are recommended. Surgical intervention should be performed in cases that do not show clinical improvement. Early recognition and treatment are essential for improving the prognosis of this devastating ocular infection.

Transparency Declaration

No conflict of interest to be declared.

References


