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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

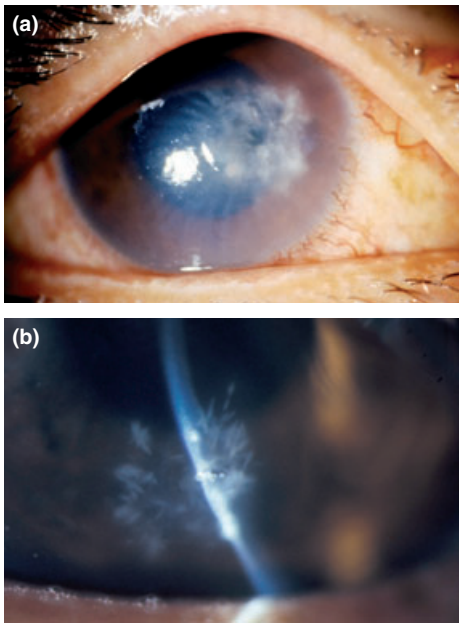

FIG. 1. Characteristic patterns of non-tuberculous mycobacterial keratitis. (a) *Mycobacterium fortuitum* keratitis showing paracentral stromal infiltrates with radiating projections, mimicking a 'cracked windshield' appearance. (b) Infectious crystalline keratopathy characterized by white, crystalline, refractile, branching stromal infiltrates.