Nocardia Keratitis

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8.1 Introduction

Corneal infection caused by rare organisms is often difficult to manage [1]. A large part of the difficulty in dealing with such an organism is a lack of a standardized method for their diagnosis, atypical presentation leading to a delay in suspicion, and a lack of standard treatment protocol. In some cases, the infection itself runs an indolent course despite being sensitive to the antibiotics used. *Nocardia* keratitis belongs to one such category of microbial keratitis, which, although the term rare may not be justified, runs an atypical course, and often associated with poor outcomes.

Nocardia, initially classified as a fungus, is now identified as a gram-positive bacteria [1, 2]. Ocular infections with *Nocardia* are rare and include keratitis, scleritis, and endophthalmitis [3]. In 1944, the first case of *Nocardia* keratitis was reported by Benedict et al., following which several case reports and few case series from various parts of the world have been reported [2–4]. The diagnosis of this entity is often missed, as the clinical picture is not well known to all considering its rare occurrence. Also, the presentation may sometimes be nonspecific or mimic other common clinical entities like fungal or atypical mycobacterial infection, further adding to the problem [2]. This results in a delayed diagnosis and improper management in most of the cases. Hence, in this chapter, we attempt to familiarize our readers with the microbiology, clinical features, investigations, and management of cases presenting with *Nocardia* Keratitis.

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S. Das, V. Jhanji (eds.), *Infections of the Cornea and Conjunctiva*,
https://doi.org/10.1007/978-981-15-8811-2_8

8.2 Epidemiology

Nocardia is ubiquitous. It is extensively found worldwide and is saprophytic. It is an essential component of the normal soil microflora as well as water. It may also be found in air, dust, and decaying vegetation [2]. Ocular infection often occurs as a result of contamination from these sources, mostly associated with ocular trauma, as *Nocardia* is not a part of the normal ocular flora. Most of the cases of *Nocardia* keratitis have been reported from Asian Countries. The prevalence of *Nocardia* keratitis varies from 1.7 to 8.3% of all cases of bacterial keratitis, as reported in studies from South India [5, 6]. Also, a rising trend has been observed in this region. However, such cases have been less commonly reported from other parts of the world. Therefore, eliciting a travel history to Asia is important in case of clinical suspicion of Nocardial infection [7]. Of the important clinical isolates, *N. asteroides* is commonly found in the temperate region and *N. brasiliensis* in the tropical and subtropical areas.

8.3 Microbiology

The taxonomy of *Nocardia* has undergone numerous revisions over the past leading to a lot of confusion and controversy [8]. Initially, all cases were referred to as *Nocardia asteroides* only; however, it was found that it is a group of bacteria with a heterozygous pattern of antimicrobial drug susceptibilities and was referred as *N. asteroides* complex. Later, *N. asteroides* complex was separated and reorganized into different species on the basis of drug susceptibility patterns. To date, more than 50 species belonging to this group have been identified. Common species identified to be of clinical significance for human infections include *Nocardia abscessus, Nocardia brevicatena-paucivorans* complex, *Nocardia nova* complex (which includes *Nocardia nova, Nocardia veterana, Nocardia africana, Nocardia kruczakiae*), *Nocardia transvalensis* complex, *Nocardia farcinica*, and *Nocardia asteroides* [8, 9]. *N. asteroides* and *N. brasiliensis* are the most common species involved in ocular infection [2, 10–12]. Other species of clinical importance are *N. farcinica*, *N. abscessus*, *N. cyriageorgica*, *N. gypsoides*, *N. levis*, and *N. caviae* [11, 13, 14].

Nocardia is a gram-positive, immobile, aerobically growing bacteria. However, it appears as a filamentous bacterium with a hyphae-like branching on direct microscopy, unlike other gram-positive bacteria. It has numerous branching with thin beaded filaments (<2.5 μm) [2, 14]. The branching is observed at the right angle. It shows variable acid fastness, largely due to variability in the cell wall mycolic acid. Both acid-fast and non-acid-fast variants of *Nocardia* have been observed with Ziehl–Neelson staining. The sensitivity for detecting *Nocardia* is 87% with gram stain and 100% with 10% KOH wet mount [15]. This microorganism does not have fastidious requirements for growth and can be cultured in conventional bacteriologic media like blood agar or chocolate agar.

8.4 Risk Factors

The risk factors for *Nocardia* keratitis are similar to other forms of infective keratitis. Ocular trauma is the most common predisposing factor as *Nocardia* is found in soil, dust, and vegetative matter [3, 11]. Sridhar et al. reported a definite history of trauma in 25% of their cases in a series, including 16 culture-proven cases of *Nocardia* keratitis [16]. Lalitha et al. reported a previous history of trauma in as high as 84% of cases in a series of 32 eyes of *Nocardia* keratitis [11]. Similarly, DeCroos et al. in the most extensive series published on *Nocardia* keratitis involving 111 cases of culture-proven *Nocardia* keratitis reported ocular exposure to soil or plant matter in 48% of their cases [3]. Next to trauma, ocular surgery accounts for most cases of *Nocardia* keratitis reported in the literature. *Nocardia* keratitis has been reported following keratorefractive surgery (LASIK/PRK), penetrating keratoplasty, implantation of intracorneal ring segments, extracapsular cataract extraction, phacoemulsification, and Descemet membrane endothelial keratoplasty (DMEK) [3, 17–20]. Other reported risk factors include contact lens wear and topical steroid use [2].

8.5 Clinical Presentation

The growth rate of *Nocardia* is relatively slow; hence, fulminant infection with this microorganism is rare. The onset is usually indolent. The progression is slow. The infection usually runs a prolonged and benign clinical course. Most cases are unilateral except the cases following refractive surgery where it can present bilaterally. Similar to other forms of keratitis, males are affected more than females [3, 16].

The most common presenting symptoms are ocular pain, redness, watering blepharospasm, and lid swelling. The pain can be out of proportion to the clinical findings. Conjunctival congestion with a papillary reaction is often noted.

Corneal involvement may occur in several forms. Most commonly, it presents as patchy infiltrates, predominantly involving the anterior corneal stroma. These infiltrates are often arranged in a characteristic "wreath-like pattern" with satellite lesions (Fig. 8.1) [3]. The adjacent epithelium and subepithelial area are also involved. An overlying epithelial defect is seen in most of the cases. The infiltrates are usually situated in the mid-periphery of the cornea. The surrounding cornea remains clear in most of the cases. It can be associated with keratic precipitates, endothelial ring deposits, anterior chamber reaction, and hypopyon. With time vessels extend from the periphery towards the lesion. Over time, the granular infiltrates may coalesce to form a grayish plaque and subsequently, a corneal ulcer. A reduced corneal sensation can be seen in some cases. However, it must be remembered that this classical picture is seen in only around 30% of the cases [3]. In few cases, the ulcer margin is surrounded by raised and multiple yellow-white "pinhead-shaped superficial corneal infiltrate." [2, 16]

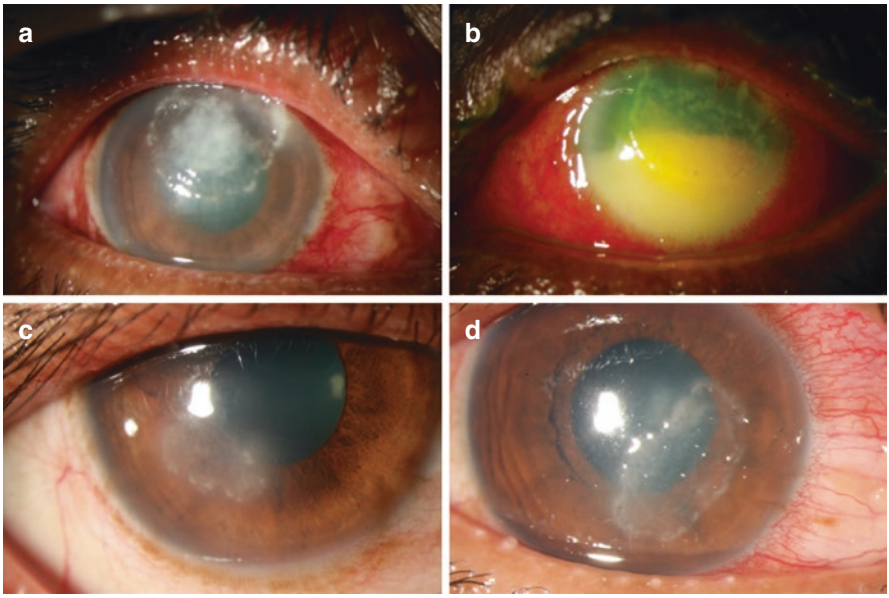

Fig. 8.1 Slit-lamp photograph showing: (**a**) superficial infiltrate with pinhead-like lesions in the periphery arranged in wreath-like pattern; (**b**) superficial infiltrate with hypopyon; (**c**) a case of *Nocardia* keratitis with superficial paracentral stromal infiltrate; and (**d**) superficial patchy stromal infiltrate. (Courtesy: Sujata Das)

Almost half of the cases of *Nocardia* keratitis present with atypical features. These include pseudo-dendritic corneal ulcer, satellite lesions, large corneal ulcer with overhanging edges, persistent epithelial defect, cotton wool appearance, full-thickness corneal infiltrate, and deep stromal infiltrate with endothelial plaque [21, 22]. Post-LASIK infections present as a well-defined whitish nodule surrounded by corneal infiltrate at the interface [18]. Lalitha et al. observed that cases presenting within 2 weeks of onset usually have a characteristic clinical presentation while those presenting later have atypical features, although a similar finding was not observed in other studies. It may be due to the fact that the atypical presentations are usually less symptomatic in contrast to the classical presentation and hence a delayed presentation.

8.6 Differential Diagnosis

Fungal and Mycobacterial keratitis is the common differentials for *Nocardia* keratitis, as all of them share an indolent clinical course [2, 11]. However, classical features of fungal keratitis, such as feathery margins, endothelial plaque, and dry look, often help in differentiating the two forms of keratitis. Likewise, infiltrates with indistinct fluffy or feather-like appearance with radiating projections in cases of atypical mycobacteria helps in differentiating it from *Nocardia* keratitis. Viral keratitis is another differential as pseudo-dendrites are sometimes seen with *Nocardia*

keratitis. Nevertheless, lack of infiltrates and rapid response to topical acyclovir often rule out *Nocardia*.

8.7 Investigations

8.7.1 Microscopy

Corneal scraping specimen is collected for microbiological investigation. Proper communication with the microbiologist regarding suspicion for *Nocardia* is essential. Microscopic examination of the prepared smears is done with gram stain, Giemsa stain, KOH stain, calcofluor white stain, and modified Kinyoun stain (1% sulfuric acid) [3]. *Nocardia* appears as a gram-positive bacteria with branching filaments having a beaded appearance [2]. *Nocardia* is partially acid-fast on modified Kinyoun stain (1% sulfuric acid); however, it completely decolorizes on treatment with 20% sulfuric acid, which helps to differentiate it from Mycobacteria [14]. KOH wet mount also reveals branching thin filaments. It is essential to emphasize here that; although *Nocardia* can be seen by various smear examinations, Gram staining is the most sensitive method for its diagnosis, and the modified acid-fast stain is not reliable. The modified acid-fast stain should be used only to confirm the acid fastness of organisms suspected to be *Nocardia* by Gram staining.

8.7.2 Culture

It is not a fastidious microorganism and hence can be cultured in conventional media like blood agar, chocolate agar, and BACTEC blood culture broth media. Selective media for *Nocardia* includes colistin-nalidixic acid agar, modified Thayer-Martin agar, and buffered charcoal-yeast extract (BCYE) and selective BCYE agars. Selective media can be used to optimize the identification of *Nocardia* when suspicion for the same is high or smear has already revealed *Nocardia*. Colonies appear by 48–72 hrs but sometimes may take as long as 2 weeks. Hence, one should wait for at least 2 weeks before declaring a negative culture to avoid a false negative report. A zone of ß-hemolysis may be observed around the colonies by third day in sheep or bovine blood agar; however, *N. asteroides* are mostly nonhemolytic in sheep blood agar [2]. Since *Nocardia* is not a part of the natural human ocular flora or laboratory environment, its growth, even on a single solid media, is considered positive, unlike other microorganisms [1]. It grows in the form of pellicle on the surface of liquid media, which breaks into small particles on shaking [2].

8.7.3 Confocal Microscopy

The use of confocal microscopy has recently been described as a noninvasive tool for the identification of Nocardial infection. It is especially useful in cases where the lesion is difficult to access for corneal scraping, such as deep corneal infiltrate with

an absence of an overlying epithelial defect, keratitis after LASIK, implantation of intracorneal ring segments, following keratoplasty, and in self-sealing wounds after cataract surgery. *Nocardia* appears as hyperreflective, short, thin, and right-angled branching filaments in the background of bright round-to-oval inflammatory cells [19, 23]. They are best visualized at the edge of the infiltrate since the scattered light from the inflammatory cells is least here [23]. These filamentous structures of *Nocardia* can be confused with other linear structures seen on confocal microscopy such as fungal filaments and corneal nerves. Fungal filaments are highly reflective, double-walled, elongated, septate with varying size between 3 to 8 μm (Nocardia, <1.5 μm), runs the entire length of the scanned image and have a uniform width with an irregular branching pattern. While, corneal nerves appear as bright, elongated, uniform (stromal nerves) or beaded (subbasal plexus) structures with acute-angled branching pattern and size between 5 and 20 μm in thickness [23].

8.7.4 Molecular Diagnostic-Based Methods

Identification of this organism at the species level requires advanced molecular tests. These tests include polymerase chain reaction (PCR) and gene sequencing with restriction endonuclease analysis of 16S rRNA gene and restriction fragment length polymorphism analysis of heat shock protein (HSP) gene, DNA sequencing, and pyrosequencing. However, the lack of availability of these testing facilities is often a limiting factor [24].

8.8 Management

Medical management with topical amikacin 2.5% is considered the first-line therapy in Nocardia keratitis [11]. Most of the species are sensitive to topical amikacin with low minimum inhibitory concentration (MIC) values compared to other drugs; however, strains resistant to amikacin have also been reported [25]. Aminoglycosides such as gentamicin and tobramycin are the second-line treatment of this infection. Cotrimoxazole, ciprofloxacin, gatifloxacin, vancomycin, and linezolid are the other treatment options for this microorganism [14, 25, 26]. Systemic treatment with cotrimoxazole has been described for cases not responding to topical therapy [25]. Complete healing with topical poly Hexa-methyl biguanide (PHMB) 0.02% has been reported in a case of *Nocardia* sclerokeratitis [27]. The mean healing time for *Nocardia* keratitis is approximately 38 days [3]. Topical corticosteroids should be avoided in these cases as they increase the risk of corneal perforation and endophthalmitis.

Medical management usually results in clinical resolution in most of the cases. However, surgical intervention is warranted in cases not responding to medical therapy or showing signs of progression despite maximum medical therapy. Lamellar keratectomy can be performed to reduce the infection load and increase the drug penetration cases showing poor response to medical treatment. Therapeutic

penetrating keratoplasty is performed for cases with full-thickness corneal ulcers, impending perforation, and perforated corneal ulcers [2, 11].

8.9 Complications

Delay in diagnosis can sometimes result in the extension of the corneal infection to cause *Nocardia* scleritis. Management of such cases often requires surgical intervention in addition to topical amikacin therapy [3]. The surgical intervention in these cases includes scleral debridement to reduce the infective load, tissue adhesive application for impending perforation, and conjunctival excision. The mean healing time is 2 months, which is much longer than that for cases with only corneal involvement [3]. Use of topical PHMB 0.02% and intravenous amikacin has also been reported for this condition [3, 27]. Nocardial infection can also result in endophthalmitis [3]. However, there are no reports of direct extension of corneal infection resulting in endophthalmitis. Management of these cases include pars plana vitrectomy with intravitreal antibiotic injection in addition to topical amikacin therapy [3]. The outcome for both Nocardia keratitis and endophthalmitis is poor. Corneal perforation as a result of a progression of keratitis is another dreaded complication of this condition that may affect the long-term visual outcome and result in blindness if left untreated.

8.10 Outcome

The variability in clinical presentation and lack of familiarity among clinicians and microbiologists with this rare condition often results in a delayed diagnosis. This delay in diagnosis, in conjunction with the lack of response of this microorganism to the routinely used antimicrobial drugs often results in variable outcomes despite the indolent course of the disease [3, 11, 16]. However, complete healing with medical treatment is observed in most of the cases.

The use of steroids is known to worsen the course of *Nocardia* keratitis and, in extreme cases, may result in corneal perforation or endophthalmitis [12, 28]. The 12-month follow-up results of steroids in corneal ulcer treatment trial (SCUT) highlighted that the use of topical steroids in *Nocardia* keratitis resulted in a relatively larger scar size when compared to the nonsteroid group while cases of non-*Nocardia* keratitis treated with steroids showed a nonsignificant reduction in the scar size [28].

Lalitha et al., in a retrospective case series of 32 patients of *Nocardia* keratitis, reported complete healing with medical therapy in 30 cases with the requirement for surgical intervention in only two cases [11]. In this study, 25% of cases were treated with sulfacetamide with or without gentamicin/ciprofloxacin, 31% of cases with gentamicin/ciprofloxacin, and 44% cases with amikacin. Visual acuity improved in 44% cases while it remained the same in 50% cases. The authors observed a faster healing rate in cases treated with topical amikacin. DeCross et al., in the largest case series of *Nocardia* keratitis (111 cases), reported complete healing with medical

therapy in 82% cases [3]. Topical amikacin 2.5% was the first line of treatment in all the cases. Systemic cotrimoxazole was added in cases of poor response to topical amikacin therapy. Surgery was performed in cases with poor response to medical treatment and cases having a large corneal ulcer, scleral involvement, corneal thinning, or corneal perforation at the time of presentation. The authors observed that younger age and better visual acuity at presentation resulted in a better final visual acuity [3].

8.11 Conclusion

Nocardia keratitis is a rare cause of infectious keratitis in the world and is more commonly found in Asian countries. It has an indolent course and is often misdiagnosed due to its atypical clinical presentation and lack of familiarity of clinicians with this condition. Pinhead-shaped superficial corneal infiltrate and wreath-like pattern of patchy anterior stromal infiltrate is typical of *Nocardia* keratitis. Gram-positive branching filamentous bacteria with 1% acid-fast staining are the key findings for its microbiological diagnosis. Topical amikacin remains the mainstay of treatment, and most of the cases respond well to medical therapy. Early diagnosis and appropriate therapy can salvage vision in most of the cases.

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