Optimizing Diagnosis and Management of *Nocardia* Keratitis, Scleritis, and Endophthalmitis: 11-Year Microbial and Clinical Overview

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Objective: To identify clinical factors and microbiological assays that facilitate a rapid diagnosis of *Nocardia* keratitis, scleritis, and endophthalmitis, and to determine optimal medical and surgical management strategies.

Design: Retrospective, consecutive case series.

Participants: A total of 111 cases of keratitis, 11 cases of scleritis, and 16 cases of endophthalmitis, all culture-proven *Nocardia* infections, were identified between January 1999 and January 2010.

Intervention: The keratitis cases underwent intensive medical management, and the scleritis and endophthalmitis cases required concurrent surgical intervention for disease control. Corneal and scleral scrapings, as well as undiluted vitreous sample, were submitted for microbiologic evaluation (direct smear and culture).

Main Outcome Measures: Historical points, clinical findings, and microbiologic assays that facilitated a prompt *Nocardia* diagnosis were identified, and management choices were examined for correlation with final acuity.

Results: Ocular exposure to soil or plant matter was a common historical point in cases of *Nocardia* keratitis (48%) and scleritis (45%), respectively. *Nocardia* keratitis often (38.7%) presented with "wreath"-shaped anterior stromal infiltrate or infiltrate interspersed with elevated, pinhead-sized, chalky lesions. Most patients with scleritis (63.4%) presented with nodular lesions demonstrating pointed abscesses. *Nocardia* endophthalmitis typically (75%) presented with endoexudates or nodular exudates surrounding the pupillary border. Gram stain and 1% acid-fast stain enabled prompt diagnosis of *Nocardia* in 64% and 63% of keratitis cases and 45% and 63% of scleritis cases, respectively. Direct smear was usually not revealing in cases of *Nocardia* endophthalmitis. Isolates from *Nocardia* keratitis, scleritis, and endophthalmitis demonstrated 97%, 100%, and 90% susceptibility to amikacin, respectively. *Nocardia* keratitis resolved with medical therapy alone in 82% of cases. Younger age and better initial acuity correlated with improved final acuity in keratitis cases. Outcomes were poor after *Nocardia* scleritis and endophthalmitis.

Conclusions: Early appropriate treatment often results in visual recovery in eyes with *Nocardia* keratitis. Despite aggressive and prompt surgical intervention, the prognosis for *Nocardia* scleritis and endophthalmitis is more guarded. *Nocardia* isolated from ocular infections demonstrate high levels of susceptibility to amikacin.

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Organisms in genus *Nocardia* are gram-positive, weakly acid-fast, filamentous bacteria that are a rare but significant cause of ocular infection. These saprophytic bacteria are ubiquitous and found in water, soil, dust, and decaying vegetation worldwide. Although *Nocardia* are not commensal organisms, they can be found as a saprophyte on the skin and upper respiratory tract.[1] Most known for causing pulmonary disease in immunocompromised patients, these organisms have been increasingly identified as a cause of ocular morbidity in immunocompetent individuals.[2–5]

Nocardia ocular infections, such as keratitis, scleritis, and endophthalmitis, are characterized by a protracted clinical course and poor visual outcomes.[3,6,7] This pathogen is frequently resistant to typical first-line ocular antibiotics, such as fluoroquinolones,[6] and delay in diagnosis can lead to suboptimal outcomes. This delayed diagnosis may be in part due to a clinician's lack of familiarity with this uncommon pathogen. In reports from multiple series worldwide analyzing keratitis,[8–12] scleritis,[13] and endophthalmitis,[14–17] *Nocardia* isolates were reported at less than 2% frequency.

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Expeditious recognition of the clinical signs of *Nocardia* infection (keratitis, scleritis, or endophthalmitis) combined with appropriate microbiologic diagnostic testing may help clinicians improve anatomic and functional outcomes. In particular, microbiologic data can facilitate both rapid diagnosis and help tailor therapy later in the clinical course. This study focuses on identifying distinctive and characteristic clinical features and appropriate microbiology tests for expeditious diagnosis of *Nocardia* infection. To this end, our group analyzed 111 cases of *Nocardia* keratitis, 11 cases of scleritis, and 16 cases of endophthalmitis. All 138 cases originated from various parts of India, and the majority began in South India.

Materials and Methods

A retrospective study of consecutive cases of *Nocardia* keratitis, scleritis, and endophthalmitis managed in an academic setting from January 1, 1999 to January 1, 2010, was performed. All patients were evaluated at the Kallam Anji Reddy campus of L V Prasad Eye Institute (Hyderabad, India) and abstracted from a computerized microbiology database cataloging all ocular infections. The study was performed with institutional review board approval (L V Prasad Eye Institute: LEC08122, Duke Eye: Pro00018692). Only culture-positive cases of *Nocardia* were included in this study.

Details collected included demographic details, nature of inciting event if any, time course until evaluation, treatment before arrival at our center, medical and ocular history, baseline clinical examination, microbiologic identification, antibiotic susceptibilities, medical and surgical treatment, clinical course, and final outcome. All cases had a detailed history and slit-lamp biomicroscopic examination. We made note of any prior trauma and surgery, including cataract surgery, penetrating keratoplasty (PK), and open globe repair. If the fundus could not be visualized, B-scan ultrasonography was performed using the 10-MHz handheld transducer looking for evidence of vitreoretinal or choroidal pathology, as well as for any intraocular foreign body.

Microbiology workup consisted of microscopic examination of smears using various staining techniques and inoculation of specimen on culture media that facilitate growth of bacteria, fungi, and *Acanthamoeba*. The specimens used for microbiology workup consisted of corneal scrapings, scleral scrapings after conjunctival excision and scleral de-roofing, or undiluted vitreous obtained during vitreous biopsy or vitrectomy. Each sample was smeared on clean presterilized glass slides for microscopic examination using Gram stain, Giemsa stain, and potassium hydroxide (KOH) with calcofluor white preparation. One percent or 20% acid-fast stains (Kinyoun stain, Ziehl-Neelsen stain) were used when there was a strong clinical suspicion of *Nocardia* or atypical mycobacterial infection.

The specimens were also inoculated onto sheep blood agar, chocolate agar, Sabouraud dextrose agar, potato dextrose agar, thioglycollate broth, brain heart infusion broth, and non-nutrient agar with *Escherichia coli* overlay (for *Acanthamoeba*). All media except Sabouraud dextrose and potato dextrose agar were incubated at 37°C for a period of 7 days. Sabouraud dextrose and potato dextrose agar were incubated at 27°C for a period of 14 days. A positive smear for *Nocardia* was defined as gram-positive thin branching filaments on Gram stain (Fig 1A, available at http://aaojournal.org) or thin branching filaments on Giemsa stain, KOH preparation, or acid-fast staining (Fig 1B, available at http://aaojournal.org). Because *Nocardia* is only weakly positive on acid-fast staining, positive acid-fast staining was not required of the filaments.

The culture was considered significant when there was (1) growth of the same organism on 2 or more media; (2) confluent growth at the site of inoculation on 1 solid media; or (3) growth in 1 medium with consistent direct microscopy findings.[18] Speciation was performed by biochemical reactions until 2007 and afterward by 16S rRNA gene sequencing.[19,20] Antibiotic susceptibility was performed using the E-test[21] (AB Biodisk, Stockholm, Sweden) for 20 isolates, and the rest were tested using the disc diffusion method.[22] Susceptibility was recorded for amikacin, cefazolin, ofloxacin, gentamicin, vancomycin, gatifloxacin, moxifloxacin, ciprofloxacin, chloramphenicol, and trimethoprim/sulfamethoxazole when available.

Initial treatment was started on the basis of smear results and modified according to clinical response, culture, and antibiotic susceptibility testing. The treatment protocol used in the institute during the study period was as follows:

Nocardia Keratitis

All patients in whom smear examination did not reveal bacteria, fungi, or parasite received treatment with topical broad-spectrum antibiotics. This was topical ciprofloxacin 0.3% or ofloxacin 0.3% monotherapy until 2002 and a combination of cefazolin 5% with ciprofloxacin 0.3% after 2002. This change was necessary in light of the decreasing efficacy of second-generation fluoroquinolones against gram-positive organisms.[12] If direct smear examination revealed acid-fast organisms or thin beaded branching filaments, the patients were administered topical amikacin 2.5%. Topical antibiotic drops were given hourly on an outpatient basis for less severe cases and on an inpatient basis for severe keratitis cases, including those with complications. The patients with *Nocardia* keratitis who showed slow response or worsening on topical amikacin were also administered oral trimethoprim/sulfamethoxazole. Resolution of keratitis was defined as lack of both epithelial defect and stromal infiltrate. Healing time was defined as time from initial presentation to complete resolution of keratitis. Surgical treatment was considered for all patients not responding to the medical treatment, presenting with large infiltrate threatening scleral involvement, or developing gross thinning or perforation. The surgical options were application of tissue adhesive and bandage contact lens or PK.

Nocardia Scleritis

Initial medical therapy was based on clinical diagnosis and direct smear results. Acid-fast organisms or thin, beading, branching filaments suggestive of *Nocardia* led to initial treatment with topical amikacin. In addition, patients with *Nocardia* scleritis received systemic therapy with intravenous amikacin or oral trimethoprim/sulfamethoxazole. Treatment was later modified on the basis of clinical response and antibiotic susceptibility of cultured isolated. Surgical debridement was performed to facilitate antibiotic penetration if necrotic tissue was thought to be impeding healing despite appropriate medical treatment of susceptible organisms. Resolution of scleritis was defined as resolution of scleral ulceration along with lack of redness and subjective report of pain. Healing time was defined as time from initial presentation to complete resolution of scleritis.

For this study, cases involving both cornea and sclera were classified as follows: (A) Eyes with large scleral lesion with contiguous corneal infiltrate and positive culture only from scleral scraping were classified as scleritis. (B) Eyes with a large corneal lesion with adjacent scleral lesion and positive culture only from corneal scraping were classified as keratitis. (C) Eyes with non-