

Nocardia Keratitis

Species, Drug Sensitivities, and Clinical Correlation

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Purpose: To correlate the clinical presentation and treatment outcome of *Nocardia* keratitis with the time to diagnosis, different species and with the drug sensitivity pattern.

Method: Patients with *Nocardia* corneal ulcers were studied at a tertiary eye care center. Speciation of *Nocardia* isolates was done by sequencing the 16s rRNA gene. Clinical response to treatment was assessed by chart review.

Results: Twenty one (65.3%) patients presented within 15 days of the onset of symptoms with typical clinical features of *Nocardia* keratitis, ie, a ring-like distribution of superficial infiltrates in a wreath pattern. Eight patients (25%) who presented after 15 days and within 30 days had an ulcer resembling fungal keratitis. *N. Cyriaciageorgica* (n = 11; 34.37%), *N. asteroides* (n = 9; 28%), *N. farcinica* (n = 7; 22%), and *N. Otitidiscaviarum* (n = 5; 16%). All the species had 100% sensitivity to amikacin, sulphamethoxazole, imipenem and co-trimoxazole. Time to diagnosis of the infection was significantly associated with the different types of clinical presentation; those presenting early having the typical clinical picture ($P = 0.004$). Patients (73%) presenting within 15 days showed a highest recovery rate. ($P = 0.045$). The recovery time of the patients when compared with species showed those who were infected with *N. cyriaciageorgica* had a healing time of less than 15 days. Clinically, healing was faster when treated with 2% amikacin. Visual outcome improved in fourteen patients (44%) and sixteen (50%) patients remained the same ($P = 0.0001$).

Conclusion: Characteristic clinical picture of *Nocardia* is dependant on early presentation. It could be mistaken for fungal keratitis. Microbiological confirmation is important. Drug of choice for *Nocardia* keratitis is amikacin.

Key Words: *Nocardia* keratitis, species, antibiotic sensitivities, clinical feature

(*Cornea* 2007;26:255–259)

Received for publication December 21, 2005; revision received September 11, 2006; accepted October 10, 2006.

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The authors state that they have no proprietary interest in the products named in this article.

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Microbial keratitis is a common and serious ocular infection.^{1,2} Although *Nocardia* species are an important cause of keratitis, they are relatively uncommon.³ *Nocardia* keratitis may be misdiagnosed clinically because of unfamiliarity or because of its clinical resemblance to mycotic or mycobacterial keratitis.⁴ The current recommended treatment is amikacin,⁵ and with appropriate therapy, *Nocardia* keratitis resolves with scarring, with or without vascularization, resulting in good visual outcome.^{3,5,6} Among the various species of *Nocardia* responsible for ocular infection, *N. asteroides* has been found to be the most common causative species for keratitis.^{3,6–11} Other species reported are *N. gypsoides*,¹² *N. brasiliensis*,¹³ *N. farcinica*,¹⁴ and *N. caviae*.³ *N. farcinica* has been associated with increased morbidity because of its inherent resistance to antibiotics.¹⁴ No large series on speciation of *Nocardia*-causing keratitis has been done. This retrospective study was performed to analyze the clinical presentation, treatment outcome, and morbidity of culture-positive cases of *Nocardia* keratitis, correlating it with various causative species of *Nocardia*. Drug sensitivity patterns of various species have also been determined.

MATERIALS AND METHODS

The institutional review board of Aravind Medical Research Foundation, Aravind Eye Hospital, and a tertiary eye care center in South India approved review of the medical records. Retrospective search of the medical record database showed 85 culture-positive cases of *Nocardia* keratitis over a period of 5 years (January 1999 to December 2003), of which 32 cases met our study criteria, which were a follow-up of ≥ 3 months and a positive culture of *Nocardia*.

The details collected from the case records included demography, risk factors, previous medication, associated ocular and systemic disorders, nature of clinical presentation, time of presentation to our hospital, microbiologic data with speciation and antibiotic sensitivity, time of complete recovery, management, and outcome at the last follow-up of the patients. All patients underwent a gross systemic evaluation and detailed clinical examination by slit-lamp biomicroscopy. On the basis of the clinical picture, keratitis was grouped as typical, atypical resembling fungal, and not consistent with any specific characteristic features. A typical clinical picture of *Nocardia* keratitis is in the form of an ulcer, with margins studded with yellow-white discrete pinhead-sized superficial infiltrate forming a characteristic wreath pattern.¹⁵ Cases with endothelial plaque or ulcers with irregular and feathery margins resembling fungal ulcers were grouped as atypical presentations.

Cases without characteristic diagnostic features of any keratitis were grouped separately as nonspecific. Clinical diagnoses were confirmed by a microbiologic examination of corneal scraping.

Corneal scraping was performed under aseptic conditions after instillation of 4% lignocaine hydrochloride under slit-lamp magnification. The scraping was done using a heat-sterilized Kimura spatula, and the material was smeared on glass slides for Gram stain and 10% potassium hydroxide wet mount. A partial acid-fast stain was done for confirmation. Culture inoculation was done on 5% sheep blood agar, chocolate agar, potato dextrose agar, and brain-heart infusion broth. All media other than potato dextrose agar were incubated at 37°C in a CO₂ incubator. Potato dextrose was incubated at 25°C. The cultures were maintained for 7 days and observed. A positive culture was defined as growth on 2 media or growth on 1 solid medium with a positive smear. The isolates were speciated by standard microbiologic methods.¹⁶ Unknown or hitherto unidentified species were stored at -70°C until further processing for species identification by polymerase chain reaction (PCR) and sequencing. The procedure for molecular methods of speciation of *Nocardia* was as follows: DNA was extracted from freshly grown *Nocardia* cultures by vortexing a suspension of the culture with glass beads, heating the suspension to 95°C for 15 minutes, and sonication. PCR was performed as previously described.¹⁷ In brief, the DNA extracted was used as template with primers BF and R2 to amplify a 550-bp region of the 5' end of the 16S rRNA gene. The amplified product was purified by QIAquick PCR purification kit (Qiagen, Valencia, CA), and the sequencing reaction was performed with the ABI Big Dye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA), using 3.2 pmol of sequencing primer BF. The sequencing products were purified using cold ethanol precipitation, and the reaction was loaded onto the ABI prism 310 Genetic Analyzer in accordance with the manufacturer's instructions (Applied Biosystems). The results of the sequence reaction were analyzed using Sequencher Version 3.0 (Gene Codes Corp., Ann Arbor, MI), and a comparison was made with the sequences obtained with GenBank.

Treatment was initiated on the basis of direct smear results of corneal scraping and modified in accordance with clinical response, culture results, and antibiotic susceptibility reports. In cases of the smear report being negative, the treatment was from the clinical diagnosis alone. The clinical response was assessed by slit-lamp biomicroscopic evaluation until the ulcer totally healed. The patients were treated as outpatients and were instructed to apply the drops on an hourly basis during the waking hours, and the duration was reduced depending on the response to healing. The patients were examined again at weekly intervals or more often if the clinical situation warranted. Each subject was examined at the slit-lamp, and the size and depth of the infiltrate were recorded at weekly intervals to the time of healing. An ulcer was considered healed by the treating physician if the epithelial defect had healed with no staining on fluorescein application and no progression of the stromal infiltration compared with the previous visit.

The drugs administered were gentamycin, ciprofloxacin, sulphacetamide, and 2% amikacin. Two percent amikacin was

prepared by diluting 1 mL (100 mg/1 mL) of parental amikacin injection in 4 mL of distilled water. A statistical analysis was carried out to determine the correlation between the healing of the ulcers with the species of *Nocardia* and with the time elapsed from the onset of the ulcer to its presentation at the hospital and the antibiotic administered. An analysis was also carried out to study the correlation of the type of clinical presentation with the species of *Nocardia* and the time elapsed from the onset of the ulcer to its presentation at the hospital. Pearson χ^2 test and Fisher exact test were used for analysis.

RESULTS

This study included 32 eyes of 32 patients with *Nocardia* keratitis. The age of the patients ranged from 3 months to 78 years (mean, 35.5 ± 17.36 years), and men made up 69% of the group (n = 22). An analysis of risk factors for developing keratitis showed that 27 patients (84%) had a history of prior corneal trauma caused by a metallic foreign body (n = 8), sand (n = 7), vegetable matter (n = 5), stones (n = 5), and an animal tail (n = 1). Twenty-five (78%) patients had prior medication in the form of antibacterial (n = 7) or antifungal (n = 8) medication and by traditional eye medicines, which included leaf juice, castor oil, sheep blood, and breast milk (n = 10). Ten (31.1%) patients were treated with both antifungal and antibacterial drugs. There was no history of any steroid medication having been used.

The onset of symptoms and the presentation of patients to the hospital ranged from 2 to 90 days (mean, 19.22 ± 19.01 days). Twenty-one (65.3%) of 32 patients who presented within 15 days (range, 2–15 days) of the onset of symptoms had typical clinical features of *Nocardia* keratitis. Of the 21, 15 (71%) had a ringlike distribution of superficial infiltrates in a wreath pattern and 5 (24%) had superficial punctate epitheliopathy. Eight patients (25%) who presented after 15 days and within 30 days had an ulcer with feathery margins and midstromal infiltrates resembling fungal keratitis. Three patients (9.38%) with a history of prior medication and who presented >30 days after the onset of symptoms had dense diffuse stromal and endothelial infiltrates without any specific clinical characteristic features. Table 1 shows the clinical profile, management, species, and outcome of the 32 patients with *Nocardia* keratitis.

Direct microscopy with Gram stain was positive in 28 patients (84.39%), and 10% KOH was positive in 22 patients (68.75%). Species identified were *N. cyriacigeorgica* (n = 11; 34.37%), *N. asteroides* (n = 9; 28%), *N. farcinica* (n = 7; 22%), and *N. otitidiscaviarum* (n = 5; 16%; Table 2). The sensitivity of the species to the various antibiotics is shown in Table 3. All the species had 100% sensitivity to amikacin, sulphamethoxazole, imipenem, and cotrimoxazole. *N. asteroides* was found to be resistant to ciprofloxacin, *N. cyriacigeorgica* was found to be resistant to ciprofloxacin and gentamycin, and *N. farcinica* was resistant to gentamycin and tobramycin.

On analyzing the different types of clinical presentation with the type of *Nocardia* species, there was no statistically significant correlation ($P = 0.127$). However, the correlation between the different types of clinical presentation and the time elapsed from the onset of the ulcer to its presentation at

TABLE 1. Clinical Features of Nocardia Species and Outcome of the Patients with Nocardia Keratitis

No	Age/Sex	Eye	Initial VA	Risk factors	Type of Presentation	Time to Presentation (Days)	Treatment Administered	Recovery Time (Days)	Species	Result	Final VA
1	38/ F	RE	20/20000	Nil	Resembling Fungus	60	Amikacin	30	N.asteroides	Healed	20/20000
2	60/ F	LE	PL	Vegetable Matter	Resembling Fungus	30	Gentamycin	25	N.asteroides	Enucleated	PL
3	55/ F	RE	20/20000	Vegetable Matter	Typical	30	Amikacin	45	N.asteroides	Healed	20/20000
4	33/ M	LE	20/20	Unknown	Typical	7	Ciprofloxacin	45	N.asteroides	Healed	20/20
5	51/ M	RE	20/40	Foreign Body	Non-specific	4	Amikacin	20	N.cyriaciageorgica	Healed	20/20
6	40/ F	LE	20/2000	Foreign Body	Typical	10	Gentamycin	45	N.cyriaciageorgica	Healed	20/40
7	59/ M	RE	NO PL	Animal	Non-specific	90	Gentamycin+ Amikacin	15	N.cyriaciageorgica	Healed	NO PL
8	33/ M	LE	20/20000	Foreign Body	Typical	30	Erythromycin	30	N.cyriaciageorgica	Healed	20/200
9	78/ M	LE	20/600	Nil	Non-specific	2	Ciprofloxacin	30	N.cyriaciageorgica	Healed	20/600
10	7/ M	RE	PL	Stick	Typical	7	Amikacin	28	N.cyriaciageorgica	Healed	20/1200
11	31/ M	RE	20/20000	Foreign Body	Typical	15	Sulphacetamide+ Ciprofloxacin	21	N.cyriaciageorgica	Healed	20/40
12	47/ F	LE	20/1200	Unknown	Typical	10	Sulphacetamide+ Gentamycin	30	N.cyriaciageorgica	Healed	20/1200
13	32/ M	LE	20/20	Nil	Typical	7	Amikacin	15	N.cyriaciageorgica	Healed	20/20
14	15/ F	LE	20/60	Mud	Typical	7	Sulphacetamide+ Ciprofloxacin	25	N.cyriaciageorgica	Healed	20/40
15	21/ M	LE	20/60	Foreign Body	Resembling Fungus	15	Gentamycin+ Ciprofloxacin	30	N.cyriaciageorgica	Healed	20/20
16	31/ M	LE	20/30	Nil	Typical	7	Gentamycin+ Ciprofloxacin	60	N.cyriaciageorgica	Healed	20/30
17	56/ M	RE	20/20000	Vegetable Matter	Resembling Fungus	15	Amikacin+ Ciprofloxacin	30	N.cyriaciageorgica	Healed	20/20000
18	27/ M	RE	20/240	Sand	Typical	15	Amikacin	30	N.cyriaciageorgica	Healed	20/30
19	27/ F	RE	20/200	Sand	Typical	10	PHMB	23	N.farcinica	Healed	20/200
20	3 Months/ M	LE	PL	Dust	Typical	30	Amikacin	30	N.asteroides	Healed	PL
21	46/ M	LE	20/120	Foreign Body	Typical	20	Gentamycin	22	N.farcinica	Healed	20/120
22	42/ M	LE	20/60	Nil	Resembling Fungus	30	Gentamycin	45	N.asteroides	Healed	20/60
23	55/ M	RE	20/20000	Vegetable Matter	Typical	15	Ciprofloxacin+ Gentamycin	75	N.farcinica	Healed	20/120
24	29/ F	LE	20/20000	Foreign Body	Typical	15	Amikacin	45	N.farcinica	Healed	20/1200
25	20/ F	RE	20/2000	Stone	Typical	15	Gentamycin+ Ciprofloxacin	60	N.farcinica	Healed	20/120
26	31/ M	LE	20/20000	Stone	Typical	30	Amikacin	45	N.asteroides	Healed	20/20000
27	64/ M	RE	20/1200	Unknown	Resembling Fungus	10	Sulphacetamide+ Ciprofloxacin	75	N.farcinica	Healed	20/1200
28	53/ F	RE	20/60	Foreign Body	Typical	10	Ciprofloxacin+ Gentamycin	10	N.asteroides	Healed	20/80
29	52/ M	RE	20/20000	Stone	Resembling Fungus	60	Ecanozole	10	N.farcinica	TPK	PL
30	55/ M	RE	20/60	Stick	Resembling Fungus	10	Natamycin	90	N.otitidscaviarum	Healed	20/40
31	18/ M	RE	20/2000	Dust	Resembling Fungus	10	Fluconazole+ Natamycin	60	N.otitidscaviarum	Healed	20/1200
32	41/ M	RE	20/30	Sand	Typical	4	Gentamycin+ Ofloxacin	20	N.asteroides	Healed	20/30

PHMB, poly (hexamethylenebiguanide) hydrochloride; PL, perception of light; HM, hand motions; FCF, finger counting.

TABLE 2. Different Species of *Nocardia* with Keratitis

<i>Nocardia</i> species	No of isolates	% Of isolates
<i>N.asteroides</i>	11	34.37
<i>N.farcinica</i>	09	28.12
<i>N.cyriageorgica</i>	07	21.87
<i>N.otitidiscaviarum</i>	05	15.62

the hospital was significant, with those presenting early having the typical clinical picture described ($P = 0.004$).

The patients (73%) who presented within a 15-day period showed the highest recovery rate, and this was significant ($P = 0.045$). The recovery time of the patients was also compared with the type of species associated with the infection, and whereas those infected with *N. cyriageorgica* had a healing time of <15 days, infections with *N. otitidiscaviarum* took >15 days to heal. However, these data did not retain statistical significance ($P = 0.948$). The other 2 species of *Nocardia* behaved similarly. Moderate to severe anterior-chamber reaction was noted in 16 patients, and hypopyon that varied from trace to 5 mm was present in 11 cases who presented 15 days after the onset of symptoms.

Nocardia keratitis in our hospital was managed differently over the years. In 1999, 8 (25%) patients were treated with sulphacetamide alone or in combination with ciprofloxacin/gentamycin. From 2000, amikacin was introduced to treat nocardial keratitis. In 2000, gentamycin and ciprofloxacin were used to treat 10 patients (31%), of whom 6 were also treated with amikacin. During 2001–2003, 2% amikacin was used as monotherapy, and 14 (44%) of our patients who received amikacin as monotherapy resolved completely. Fisher exact test ($P = 0.556$) did not show any correlation between the time to heal and the drug administered. However, clinically, the ulcers were found to have a faster healing response in patients presenting early and combined with 2% amikacin treatment. On the whole, 16 (50%) patients healed completely between 15 and 30 days of treatment, and the recovery period ranged from 10 to 90 days, with a mean of 36 days. Thirty patients healed completely with medical treatment. One patient needed therapeutic keratoplasty, and in 1 patient, the eye was enucleated. Ulcers healed in 26 patients (81%) without vascularization, whereas 4 of them had a vascularized scar.

Eleven patients (34%) who presented with initial uncorrected visual acuity of 20/20–20/120 maintained the

same vision after treatment, and of 15 patients (47%) with 20/1200 initial visual acuity, 4 showed an improvement of 1 line on the Snellen visual acuity chart, and an improvement of 3 lines was seen in another 4 patients. Comparing the visual outcome pretreatment and posttreatment, visual outcome improved in 14 (44%) patients and 16 (50%) patients remained the same ($P = 0.0001$).

DISCUSSION

This study was undertaken to understand the types of clinical presentation and study the correlation between the species of *Nocardia* associated with ulcers and antibiotic sensitivity and to study the healing response in association with the species and with the antibiotics used over time. Corneal trauma was the major risk factor in our series, and this has been a similar experience with other researchers.^{1,3,5} Predisposing factors such as contact lens,^{6,18} topical corticosteroids,^{16,18} and prior ocular surgery¹⁹ that have been associated with *Nocardia* keratitis were not seen in our series.

This study identified 2 new species of *Nocardia* (*N. cyriageorgica* and *N. otitidiscaviarum*) associated with keratitis. *Nocardia* is a soil saprophyte and is made up of many species, and these 2 species reported by us might be endemic in the soil of South India. We did not find any of the other commonly reported species such as *N. gypsoides*, *N. brasiliensis*, or *N. caviae*. The healing response in our study was the same, irrespective of the species. This finding is contrary to what has been reported, mainly that *N. farcinica* is associated with high morbidity.¹⁴

The sensitivity pattern that was seen in this series for all the species of *Nocardia* was consistent with the reported literature. The sensitivities of *Nocardia* species revealed that all the species had 100% sensitivity to amikacin, sulphamethazole, and imipenem. Hussain et al²⁰ reported antibiotic sensitivity of 6 isolates of *Nocardia* from cases of *Nocardia* keratitis. All their isolates were sensitive to trimethoprim-sulfamethoxazole and amikacin. They suggested that these were the most reliable and effective drugs in the management of *Nocardia* keratitis. Sridhar et al,²¹ in their study of 7 patients with *Nocardia* keratitis for whom analysis of minimum inhibitory concentration was done, showed that the minimum inhibitory concentration for amikacin was low and that for ciprofloxacin was high, and their cases responded to amikacin. We agree with these findings, and although *Nocardia* shows sensitivity to many drugs, clinical experience shows that amikacin is an effective

TABLE 3. Sensitivity of 32 *Nocardia* Isolates from Keratitis

Species	<i>N.asteroides</i>	<i>N.farcinica</i>	<i>N.cyriageorgica</i>	<i>N.otitidiscaviarum</i>
No of species	9	7	11	5
Amikacin	100%	100%	100%	100%
Gentamicin	88%	0%	57.14%	100%
Tobramycin	100%	0%	100%	100%
Cefotaxim	75%	0%	85.74%	100%
Cotrimoxazole	100%	100%	100%	100%
Imipenem	100%	100%	100%	100%
Sulpha-methazole	100%	100%	100%	100%
Ciprofloxacin	0%	100%	14.28%	100%

drug in this disease. Prajna et al²² have also shown that 0.02% poly(hexamethylene biguanide) hydrochloride is effective in the treatment of *Nocardia* keratitis associated with scleritis.

The important result of this study is that the characteristic clinical features and timely response to the appropriate treatment depended on early diagnosis and initiation of treatment. We found that only the patients who presented within 2 weeks of the onset of symptoms had the typical feature suggestive of *Nocardia* keratitis, which is a ringlike superficial infiltrate in a wreath pattern, as reported in the literature.¹⁵ Although rare, this type of presentation might be seen with fungal etiologies, as has been reported.²³ Again, in this series of patients (patients 29, 30, and 31; Table 1) for whom the microscopy was negative and the clinical picture resembled a fungal ulcer, antifungal medication was started. However, the medication was changed once the culture report showed *Nocardia*. For patients 15, 17, and 22 (Table 1), even though the clinical picture showed a resemblance to a fungal ulcer, the microscopy was positive for *Nocardia* filaments. Therefore, the patients were administered antibiotics from the beginning of the treatment. Thus, *Nocardia* keratitis might resemble fungal keratitis and vice versa. This possibility emphasizes the need for cultures in corneal ulcers, especially from regions that have a high proportion of ulcers of varied etiology. A high index of suspicion should be kept in mind when treating ulcers of long duration and more so in geographic areas where the incidence of fungal keratitis is high.

Thirty patients in our series responded well to medical treatment, whereas 2 of them needed surgical intervention. *N. cyriacigeorgica* caused infection in both of these cases. However, because the remaining 9 patients infected with this species had a favorable outcome, we do not feel that this species is associated with a high morbidity. The outcome of the cases in this series was generally good. Most patients improved their visual acuity. This finding corroborates the other reports, which indicate that there is good visual recovery in the range of 20/30–20/15.^{5,6,24,25}

In summary, we reported on 2 additional species of *Nocardia* associated with corneal ulcers. The clinical presentation did not have any bearing on the type of species. *Nocardia* ulcers in general have a good prognosis, but early referral and definite diagnosis by culture are essential to start specific therapy. Amikacin can be used as monotherapy in the treatment of these cases.

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