Diagnosis, Clinical Presentations, and Outcomes of *Nocardia* Endophthalmitis

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• PURPOSE: To describe the clinical presentations, diagnosis, and management outcomes of *Nocardia* endophthalmitis.

• DESIGN: Retrospective, interventional, multicenter case series.

• METHODS: The study was conducted in a multicentric institutional practice setup and included 25 eyes of 25 patients with culture-proven *Nocardia* endophthalmitis. Anterior chamber fluid and/or vitreous and/or intraocular lens were submitted for microbiological evaluation in all cases. Patients with non-*Nocardia* etiology and those that were culture negative were excluded. Case records were studied and data regarding demography, clinical presentations, interventions received, and final visual and anatomic outcomes were noted. The main outcome measures were final visual outcomes and factors determining them.

• RESULTS: The mean age of the patients was 54.7 ± 22.9 years. By the etiology of infection, 18 (75%) eyes were post–cataract surgery (operated elsewhere), 3 (12.5%) eyes were posttrauma, and 3 (12.5%) eyes were endogenous. The final follow-up was a mean of 14.25 ± 30.35 months, median 2 months. The odds of a favorable outcome were 42.5 (95% confidence interval [CI] 3.15 to 571.84, $P = .0047$) when the vision was more than hand motions at presentation, 9.42 (95% CI 0.92 to 95.89, $P = .05$) in male sex, 21 (95% CI 0.9 to 489.7, $P = .05$) when presentation was within 48 hours, and 2.5 (95% CI 0.23 to 26.48, $P = .44$) with primary vitrectomy instead of a biopsy. The in vitro susceptibility was poor for vancomycin and was best for amikacin.

• CONCLUSIONS: The visual outcome in *Nocardia* endophthalmitis is very guarded when presenting vision is poor. On diagnostic confirmation or high index of suspicion, intravitreal amikacin is preferred. (Am J Ophthalmol 2019;197:53–58. © 2018 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Sep 8, 2018.

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NOCARDIA ARE AEROBIC, GRAM-POSITIVE, WEAKLY acid-fast filamentous bacteria. They are saprophytes commonly found in soil, water, and decaying matter. Keratoconjunctivitis owing to *Nocardia* was the first ocular infection noted in 1944.[1] Intraocular *Nocardia* infections generally occur owing to an endogenous cause, though such exogenous causes as postsurgery and posttrauma have been reported.[2–5] In general, *Nocardia* endophthalmitis carries a poor prognosis.[3,5] This may be owing to atypical and uncommon presentations and also because of lack of an index of suspicion causing a delay in diagnosis. As literature on *Nocardia* endophthalmitis is relatively sparse, in the current communication we describe our experience with *Nocardia* endophthalmitis, its clinical presentations, its demographic profile, diagnosis, and management outcomes.

METHODS

THIS STUDY IS A RETROSPECTIVE INTERVENTIONAL CASE SERIES. The study included all cases diagnosed as *Nocardia* endophthalmitis at 2 locations (Hyderabad and Bhubaneswar) of the LV Prasad Eye Institute in India. The study protocol was approved by the institutional review board. Microbiological records of all cases of infectious endophthalmitis seen between January 1, 2005 and December 31, 2017 were examined and patients with culture-proven *Nocardia* endophthalmitis were identified (Figure 1). The medical records of the patients were retrieved from the medical records department. The collected demographic information included the etiology of the infection, interval from the inciting event to the start of symptoms, interval between the start of symptoms and treatment intervention, comorbid systemic illnesses, visual acuity at presentation, detailed biomicroscopic examination including information on media clarity on indirect ophthalmoscopy, retinal examination, ultrasound findings, treatment provided, and final visual and anatomic outcomes. Cases attributed to an endogenous cause underwent blood culture and urine culture to pick up any possible

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.09.007

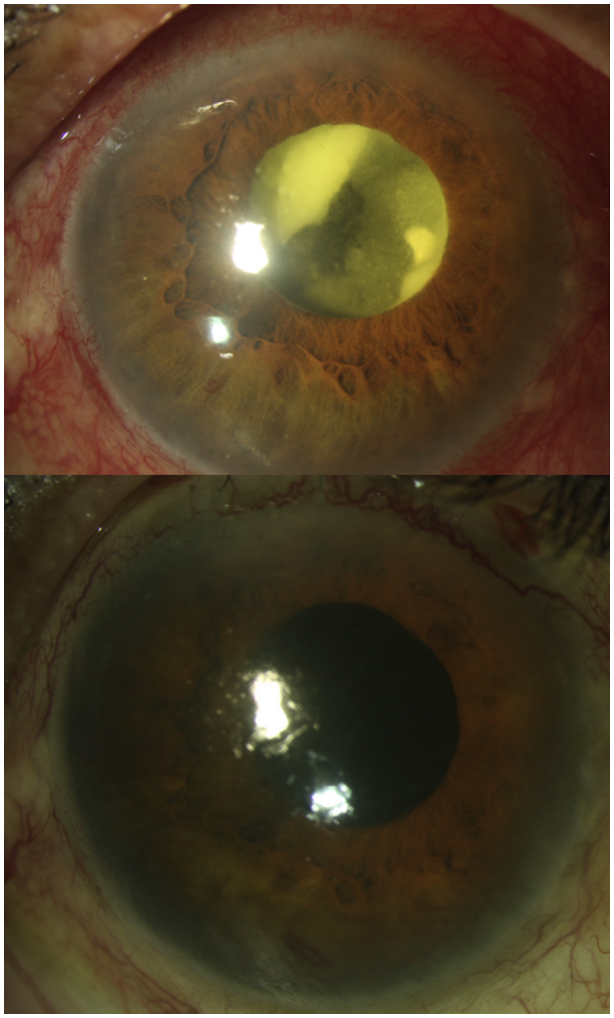

FIGURE 1. ***Nocardia*** **endophthalmitis. (Top) Preoperative clinical. (Bottom) Postoperative clinical photograph.**

TABLE 1. Baseline Demographic and Clinical Features of *Nocardia* Endophthalmitis

Feature	Result
Total eyes included	25
Age (y), mean ± SD/median (range)	54.7 ± 22.9/63.5 (6-88)
Etiology of infection, n (%)	19 (75%) postcataract 3 (12.5%) posttrauma 3 (12.5%) endogenous
Interval between inciting event and start of symptoms (d), mean ± SD/median (range)	24.23 ± 17.15/28 (4-60)
Interval between the start of symptoms and presentation to the clinic (d), mean ± SD/median (range)	13.58 ± 30.2/7 (2-150)
Cases with concurrent corneal infiltrates/anterior chamber exudates, n (%)	19 (76%)
Favorable vision at presentation, n (%)	5 (20%)
Favorable vision at last follow up, n (%)	6 (24%)

systemic focus of infection. Also in these cases, history was revisited to rule out any past history of intravenous fluid infusions or intravenous narcotics.

Management of the patients depended on their clinical presentation. Patients with milder presentations or with poor corneal clarity underwent vitreous biopsy. Those with severe vitritis as confirmed clinically or on B-scan underwent pars plana vitrectomy wherever the corneal clarity allowed. All patients were initially empirically treated with intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) after collection of the vitreous sample. The vitreous sample was collected from the mid vitreous cavity with a 2 cc syringe plugged into the suction tubing of the vitreous cutter on cutting mode and before opening the infusion fluid. Further injections were based on the culture report. If no response was noted, a repeat intravitreal injection or a pars plana vitrectomy was done after 48-72 hours, depending on the corneal clarity. In some patients anterior chamber (AC) fluid and the explanted intraocular lens were also processed.

Vitreous samples were transported to the microbiology laboratory immediately and examined by direct microscopy (calcofluor white, Gram, Giemsa stains) and culture (aerobic and anaerobic). Cases with corneal infiltrates underwent corneal scrapings, which were made into smears for direct microscopy and also inoculated on 5% sheep blood agar, 5% sheep blood chocolate agar, brain heart infusion broth, thioglycollate broth, and Sabouraud dextrose agar (SDA). All media were incubated at 37 C for 1 week except SDA, which was incubated at 25 C for 2 weeks for fungal isolation. For direct microscopy the smears were stained using Grams stain, 10% potassium hydroxide with 0.1% calcofluor white and modified Ziehl-Neelsen stain using 1% H_2SO_4. Growth on 2 or more media or confluent growth on at least 1 solid medium at the site of inoculation or growth on 1 medium with consistent direct microscopy result was defined as a significant positive culture. The culture isolates were further identified with biochemical tests.

After the initial surgical intervention, the patients received topical antibiotics (ie, ciprofloxacin 0.3%), cycloplegics, and topical steroids. Systemically the patients were administered oral ciprofloxacin 750 mg twice a day for a period of 2-3 weeks. The outcome at the last visit was evaluated in terms of anatomic and functional outcome. A favorable anatomic outcome was defined as preservation of the globe, absence of hypotony, attached retina, and absence of active inflammation at the last visit. A functional success was defined as an attached retina with a vision of ≥20/400 at the last visit.

• **STATISTICAL ANALYSIS:** The data were arranged on an Excel spreadsheet. Relevant statistical analysis was done

TABLE 2. Factors Affecting the Visual Outcome at the Final Follow-up Visit

Factor	Odds Ratio	95% CI	*P* Value
Vision more than hand motions at presentation	42.5	3.15 to 571.84	.0047
Presentation within 48 hours	21	0.9 to 489.7	.05
Male sex	9.42	0.92 to 95.89	.05
Initial intervention vitrectomy instead of vitreous biopsy	3.38	0.15 to 74.35	.43

TABLE 3. Clinical Samples With Culture Positivity for *Nocardia*

Type of Sample	Number of Samples Positive[a]
Anterior chamber tap	10
Vitreous	15
Explanted intraocular lens	3
Corneal scrapings	4
Iris tissue	2
Eviscerated content	1

[a]Multiple samples showed growth of *Nocardia* from some patients.

using MedCalc ver 18 (MedCalc Software, Ostend, Belgium). For statistical analysis, vision was converted from Snellen to logMAR equivalents. Means and standard deviations were computed for all continuous variables. In case of nonparametric distribution, median was calculated. Preoperative and postoperative data were compared using the paired *t* test in parametric data and Wilcoxon rank sum test in nonparametric data. Odds ratios were computed for the possible risk factors for endophthalmitis with appropriate confidence intervals (CI). A *P* value of $< .05$ was assigned as statistically significant.

RESULTS

THE STUDY INCLUDED 25 EYES OF 25 PATIENTS. THE AVERAGE age of the patients was 54.7 ± 22.9 years, median age 63.5 years, range 6-88 years. Baseline demographic features of the cases are summarized in Table 1. Favorable vision at presentation was seen in 5 cases and that at the last follow-up was seen in 6 cases. None of the eyes either clinically or on B scan ultrasound examination had a retinal detachment at presentation. An open globe injury at presentation was seen in 3 eyes and was repaired in the primary intervention.

Various factors that could possibly affect the outcome were assessed. The odds of a favorable outcome were 42.5 (95% CI 3.15 to 571.84, $P = .0047$) when the vision was more than hand motions at presentation, 9.42 (95% CI 0.92 to 95.89, $P = .05$) when the sex was male, 21 (95% CI 0.9 to 489.7, $P = .05$) when presentation was within 48 hours, 2.5 (95% CI 0.23 to 26.48, $P = .44$) when the initial intervention was vitrectomy instead of a vitreous biopsy alone, and 3.38 (95% CI 0.15 to 74.35, $P = .43$) when the etiology was nontrauma. (Table 2).

In microbiologic evaluation, smear for gram-positive filaments was positive in 4 of 23 (17.39%) vitreous or AC samples received (2 samples were only intraocular lenses and smear could not be prepared). Culture was found positive in all cases but different clinical samples (Table 3). Figures 2–4 show colony characteristics of the microbiologic growth seen.

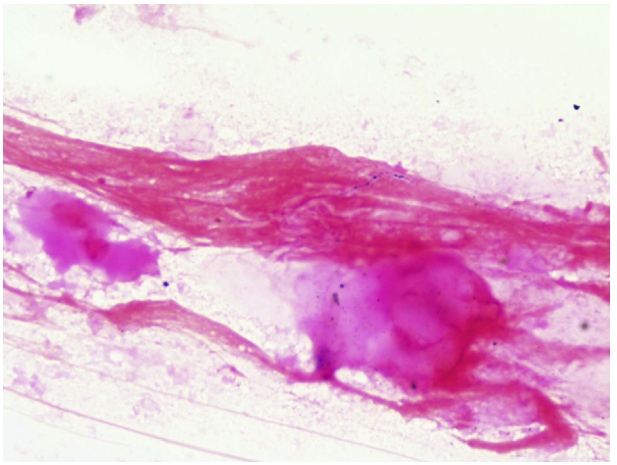

FIGURE 2. Microscopic examination of the corneal scraping shows gram-positive, thin, beaded branching filaments (Gram stain; magnification: 1000×).

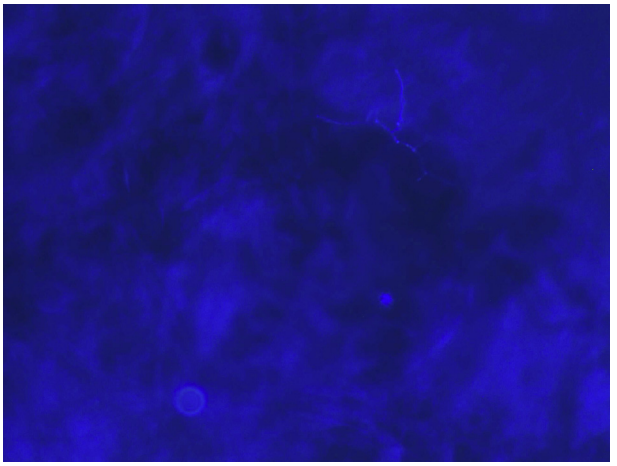

FIGURE 3. Microscopic examination of the corneal scraping shows thin, nonfluorescent, branching filaments (potassium hydroxide with calcofluor white stain; magnification: 400×).

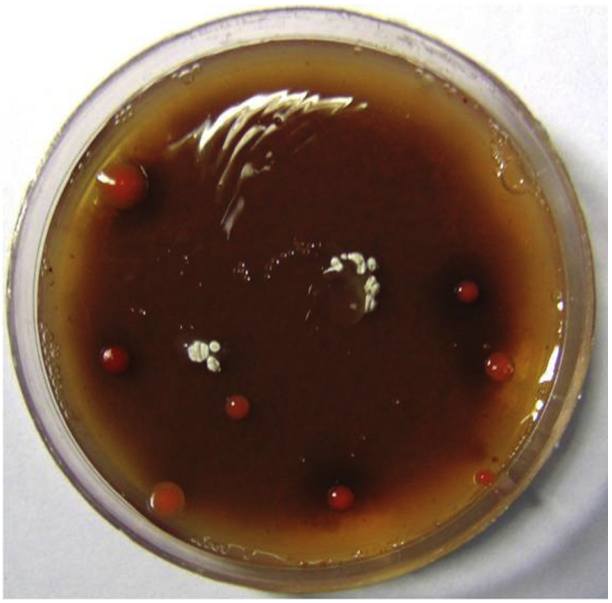

FIGURE 4. Chalky white, dry, raised, rough colonies at the edge of the intraocular lens (chocolate agar, 6 days incubation at 37 C). Red colonies are contaminants.

The antibiotic susceptibility pattern was tested against various antibiotics. One case had a positive corneal scraping on smear and culture but the vitreous was negative on culture. In descending order, the highest sensitivity was against amikacin (100.0%), followed by gatifloxacin and ciprofloxacin (87.5%), moxifloxacin (75.0%), ofloxacin (66.0%), gentamicin and chloramphenicol (54.0%), and finally vancomycin (50%) (Table 4). Only 3 of 25 eyes had an unfavorable anatomic outcome, of which 2 developed phthisis and 1 had recurrent inoperable retinal detachment. Thus overall anatomic success was achieved in 88% of the cases. The complications limiting the overall visual outcome, noted at the last visit, are summarized in Table 5.

The 3 posttraumatic cases had a mean age of presentation of 25.66 ± 18.44 years (median 21 years). All 3 cases had injury with vegetative matter. All of them had an unfavorable visual outcome, with 1 of the eyes requiring an evisceration. The 3 cases diagnosed as endogenous endophthalmitis had a mean age of presentation of 17.33 ± 16.62 years (median 15 years). None of them had a systemic focus of infection evident on systemic evaluation. One of the 3 had a favorable outcome at the last visit.

DISCUSSION

NOCARDIA ENDOPHTHALMITIS IS A RELATIVELY UNCOMMON form of endophthalmitis seen in the clinic. Among the 12 or so species of *Nocardia* known to cause infections, *Nocardia* asteroides is the commonest.[6] Because of the relatively uncommon occurrence, studies describing this entity are very sparse. *Nocardia* most commonly occurs in immunocompromised states.[7,8] In our series, though, only 1 patient had systemic immunosuppression (human immunodeficiency virus [HIV] seropositivity). In a previously reported large series of 24 cases, no case was known to have immunosuppression.[5] Decroos and associates, also from South India, had reported a series of 16 culture-positive cases of *Nocardia* endophthalmitis.[9] In that reported series, three quarters of the patients presented with AC fluffy exudates on the corneal endothelium and nodular deposits on the pupil margin. In our series 20 of 25 patients (80%) showed similar exudates. Other existing literature on *Nocardia* endophthalmitis is restricted to isolated case reports.[10–14]

Aravind and associates in their study[5] found that the AC aspirate showed significantly more positivity for *Nocardia* as compared to the vitreous aspirate. They hypothesized the higher occurrence in the AC aspirate to be occurring because of the preferential proliferation of the organism in the AC as compared to the vitreous cavity. In contrast, in the current study, the culture positivity of the AC fluid was significantly low while that of the vitreous sample was significantly high (Table 6). The sensitivity of the

TABLE 4. Comparison of the Relative Antibiotic Susceptibility Results With Previous Literature

	Antibiotic Sensitivity		
Antibiotic	Haripriya et al[5]	Current Study	*P* Value for Difference
Amikacin	87.5%	100.0%	.07
Cefazolin	4.17%	16.6%	.7
Cefotaxime	41.67%	NT	NA
Chloramphenicol	50%	54.0%	.8
Ciprofloxacin	75%	87.5%	.29
Gentamicin	50%	54.0%	.82
Norfloxacin	41.67%	NT	NA
Ofloxacin	83.3%	66.0%	.19
Tobramycin	33.33%	NT	NA
Vancomycin	12.5%	50.0%	.22

NA = not applicable; NT = not tested.

TABLE 5. Complications Noted at the Final Follow-up

Complication	Number of Eyes
Phthisis bulbi	2
Epiretinal membrane	1
Optic atrophy	2
Corneal leucomatous scarring	7
Recurrent retinal detachment	1
Glaucoma	2

TABLE 6. Comparison of Post–Cataract Surgery *Nocardia* Endophthalmitis in the Current Series With That of Haripriya and Associates

	Aravind et al	Current Series	*P* Value	95% CI for the Difference
Number of eyes	24	19		
Male sex, n (%)	15 (62.5%)	10 (52.63%)	.51	
Presentation within 1 week, n (%)	15 (62.5%)	11 (57.89%)	.76	
Favorable vision[a] at presentation, n (%)	4 (16.67%)	2 (10.52%)	.56	
Wound infiltrate, n (%)	12 (50%)	16 (84.21%)	.02	5.58%–55.43%
Hypopyon, n (%)	10 (41.66%)	17 (89.47%)	.001	19.24%–66.66%
AC aspirate positivity, n (%)	15/16[b] (93.75%)	10/19 (52.63%)	.008	11.30%–62.66%
Vitreous positivity, n (%)	1/22[b] (4.54%)	15/19 (78.94%)	<.0001	46.22%–87.49%
Favorable vision at last follow-up, n (%)	3 (12.5%)	5 (26.31%)	.25	

AC = anterior chamber.
[a]Favorable vision in the study is defined as vision ≥ 20/400.
[b]Only limited cases underwent the particular sample processing.

antibiotics as per Haripriya and associates[5] is compared in Table 4 with the current study. While the susceptibility to amikacin was noted to be very high (87.5%), that for vancomycin was very low (12.5%). Our study showed similar results. The poor sensitivity of vancomycin against *Nocardia* despite *Nocardia* being gram-positive could be owing to the fact that vancomycin acts on peptidoglycan units in the cell membranes, whereas *Nocardia* have predominantly mycolic acid in their cell walls. Conversely, amikacin interferes with protein synthesis and thus is effective against *Nocardia*.[6] Zimmerman and associates[10] had noted the clinical presentations of *Nocardia* endophthalmtis to be a delayed-onset, indolent infection akin to low-virulence organisms. Conversely, in the other large study, Aravind and associates had noted 23 of 24 of their cases to present within 6 weeks of surgery, which according to the Endophthalmitis Vitrectomy study criteria could be classified as an acute presentation. In the current study, too, we had all presentations occurring within 6 weeks of the inciting event, with a mean interval of 25 days. The possible explanation for the relative acute presentation in the Indian demography could be the relative high load of the organism in the environment locally. The overall poor prognosis can also be attributed to the fact that diagnosis is often late owing to nonfamiliarity with the organism in routine microbiologic practice. As the clinical picture with fluffy exudates often mimics a fungal etiology—especially dematiaceous fungi, in view of the brownish exudates in the AC—these cases are often initially erroneously diagnosed as fungal endophthalmitis. Initial management on those lines may cause deterioration and overall poor treatment outcomes.

Three cases in the current series were posttrauma. *Nocardia* as an etiology posttrauma is not widely reported in literature. This possibly could be owing to difficulties in diagnosis and also owing to relative variation in the prevalence of *Nocardia* in the environment the world over. Compte and associates[15] reported a case of *Nocardia* endophthalmitis after trauma, which was injury with a vegetative matter. The visual acuities, both at presentation and at final visit, were favorable. In our series too, all the cases following trauma had a history of injury with a vegetative matter.

Endogenous endophthalmitis following *Nocardia* also has been reported.[3,7,8,16–19] The cases reported in the literature either had a systemic focus of infection or had an underlying disease that required systemic immunosuppression. In our series there were 3 cases with endogenous *Nocardia* endophthalmitis. Of these, 1 was seropositive for HIV infection, whereas the other 2 were apparently healthy. None of them had a history of steroid abuse. In sync with the previous literature, our cases of endogenous origin had severe vitritis out of proportion to the anterior segment involvement.

This series had patients treated empirically with a combination of vancomycin and ceftazidime and then further with appropriate antibiotics according to the susceptibility results. Our laboratory results and also existing literature show a good susceptibility of *Nocardia* species to other antibiotics like gatifloxacin, moxifloxacin, imipenem, linezolid, and cephalosporins. As this is a severe and uncommon infection, there may be a merit in considering 1 of these higher antibiotics for the treatment in cases where *Nocardia* is isolated.

The current study also has a few inherent limitations. The effect of various confounding factors could not be independently assessed owing to the retrospective nature of the study. The limited sample size did not allow us to reach a statistical significance of the impact of certain factors. Though these factors could potentially impact the outcome, the current study does not conclusively draw any such conclusions for the possible lack of an adequate sample size. A proportion of cases of endophthalmitis in this series were posttrauma. Trauma itself is a confounding

factor for a final poor visual outcome. Thus it would be difficult to clearly delineate, in the posttraumatic subset, whether the poor visual outcome is owing to trauma or to the subsequent endophthalmitis. The antibiotic susceptibility, as reported in the current communication, has been done by the Kirby-Bauer disc diffusion method. This is one of the limitations of the study, as the best way to determine antibiotic sensitivity would be to measure the minimum inhibitory concentration levels, which could not be done owing to cost logistics.

In conclusion, *Nocardia* endophthalmitis is a relatively rare but potentially devastating ocular condition. Fluffy nodular exudates in the AC can serve as a clinical clue to the possible *Nocardia* etiology. AC tap can serve as a good modality to diagnose the etiology in cases where vitreous access is difficult. Unlike systemic nocardiosis, ocular *Nocardia* infection can occur without systemic immunocompromise. Though visual prognosis overall is not favorable, the odds of a favorable outcome increase when the vision is more than hand motions at presentation, when the patient is male, and when presentation is within 48 hours of the inciting event. Anatomic outcome, however, is overall much favorable. Amikacin can serve as a drug of choice for intravitreal injections, as it shows a very favorable susceptibility pattern towards *Nocardia*.

FUNDING/SUPPORT: THE CURRENT RESEARCH WAS SUPPORTED BY THE HYDERABAD EYE RESEARCH FOUNDATION, HYDERAbad, India. Financial Disclosures: The following authors have no financial disclosures: Vivek Pravin Dave, Avinash Pathengay, Savitri Sharma, N Naveen, Soumyava Basu, Rajeev R. Pappuru, and Taraprasad Das. All authors attest that they meet the current ICMJE criteria for authorship.

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