



Case report

Nocardial scleritis: A case report and a suggested algorithm for disease management based on a literature review



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ABSTRACT

Purpose: To report a case of nocardial scleritis and to propose a logical treatment algorithm based on a literature review.

Observations: It is important to suspect a nocardial infection when evaluating anterior unilateral scleritis accompanied by multiple purulent or necrotic abscesses, especially in male patients with a history of chronic ocular pain and redness, trauma inflicted by organic materials, or recent ophthalmic surgery. A microbiological investigation is essential. In positive cases, a direct smear reveals weakly acid-fast organisms or Gram-positive, thin, beading and branching filaments. Also, the organism (usually) grows on blood agar and Lowenstein–Jensen plates. An infection can generally be fully resolved by debridement of necrotic areas and application of topical amikacin drops accompanied by systemic sulfamethoxazole–trimethoprim.

Conclusions and significance: Together with the case report described, we review data on a total of 43 eyes with nocardial scleritis. Our proposed algorithm may afford a useful understanding of this sight-threatening disease, facilitating easier and faster diagnosis and management.

1. Introduction

Nocardial scleritis is an insidious and painful infection potentially associated with a devastating outcome.^{1–4} The differential diagnosis includes systemic autoimmune diseases, metabolic disorders, and other inflammatory/infectious conditions. It is especially difficult to distinguish the infection from those caused by fungi and other aerobic *Actinomycetales* such as non-tuberculous *Mycobacterium*.^{4,5} This is because the disease course is long, the clinical signs are nonspecific, the possible predisposing factors include ocular trauma inflicted by organic materials, and microbiological analysis is difficult.^{5,6} Furthermore, clinical treatment can be very challenging; no well-established consensus exists.⁷ It is essential to recognize the clinical features and know what to expect microbiologically when seeking to standardize treatment.

Nocardia constitute a genus of saprophytic bacteria usually found in soil, water, dust, and decomposing matter.^{1,2,9–11} *Nocardia* are not part of the normal ocular flora, and may cause keratitis, scleritis, and endophthalmitis.² In India, a developing agriculture-based economy,

Nocardia are the second most prominent cause of scleritis (20%).⁸ There has been a global increase in the number of ocular infections caused by *Nocardia*.^{8,9} Delayed diagnosis of nocardial scleritis, perhaps attributable to unfamiliarity with the pathogen, and the daunting treatment, have been inadequately addressed.^{2,4,10} The appropriate diagnostic microbiological techniques, the species involved, and possible alternatives for treating cases of drug-resistance remain poorly understood.

Here, we present a case report and a brief review of all case reports of culture-proven nocardial scleritis or sclerokeratitis published from 1900 to 2015 as identified by searching PubMed (National Library of Medicine), Scielo (Scientific Electronic Library Online), and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde). We describe the clinical features, etiology, microbiological diagnosis, and management of the condition. We derive a clinical algorithm allowing easier recognition of the disease and guiding decisions at key interventional points.

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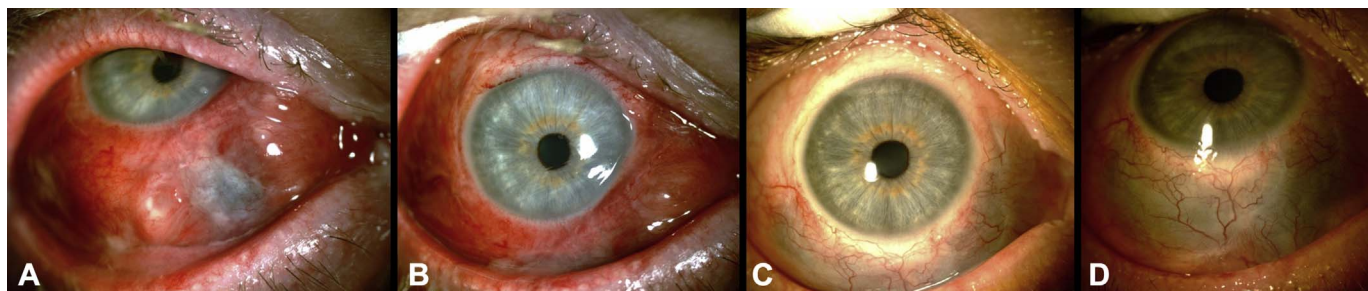


Fig. 1. Anterior biomicroscopy of a right eye with a *Nocardia pseudobrasiliensis* infection. First appointment: A. In the primary position, the eye exhibits diffuse hyperemia of the conjunctiva and cornea, with Descemet folds. B. The eye positioned to show the multifocal abscesses and the area of necrosis. Last appointment: C. In the primary position, the eye exhibits resolution of the infection but residual scleral thinning. D. In the up-gaze position, the abscesses and the necrosis are seen to have resolved.

2. Case report

A 49-year-old Caucasian house-builder was referred to our hospital with complaints of pain and redness of the right eye 1 month in duration. He reported that 2 weeks earlier a fly had flown into his eye while he was driving. His best-corrected visual acuity (BCVA) was 20/60 in the right eye (OD) and 20/20 in the left eye (OS). Intraocular pressure (measured using Goldmann tonometry) was 2 mmHg in the OD and 14 mmHg in the OS; pupillary reflexes and extraocular eye movement were normal. Slit-lamp biomicroscopy of the OD revealed 2+ / 4 + eyelid edema, 3+ / 4 + diffuse conjunctival hyperemia, and scleral nodular bulges 4 mm diameter at the 4- and 8-o'clock positions with circumscribed, whitish abscesses surrounded by necrotic tissue and avascular scleral thinning. A Descemet's fold was evident on the superior temporal cornea, but no epithelial defect or cells in the anterior chamber were found. Fundoscopy was normal (Fig. 1 a,b).

We suspected infectious necrotizing scleritis and screened for infectious and rheumatological diseases. We scheduled chest radiography, urine analyses, serum chemistry tests (which may indicate renal dysfunction in patients with systemic vasculitides), syphilis serology (FTA-ABS and RPR) tests, antineutrophil cytoplasmic antibody (ANCA) testing, evaluation of rheumatoid factor and antinuclear antibody levels, and the purified protein derivative (PPD) skin test; all were negative.

Ultrasound biomicroscopy revealed nodular thickening of the sclera at 3–4 and 8 o'clock, with scleral hyporeflexivity, and a staphyloma from 5 to 7 o'clock. B-scan ocular ultrasonography ruled out posterior scleritis. Direct smears of scrapings revealed delicate Gram-positive rods and partially acid-fast rods upon Ziehl-Neelsen staining. Bacterial colonies grew in Lowenstein–Jensen medium and on blood, chocolate, and Sabouraud agar plates (Fig. 2). Initial microbial tests identified only a member of the *Actinomycetales* order. Phenotypic tests were required to identify the pathogen. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF) was unable to identify the pathogen. PCR-restriction enzyme analysis (PRA) of the hsp65 gene identified three isolated colonies as *Nocardia pseudobrasiliensis*.¹¹

Drug minimal inhibitory concentrations (MICs) were calculated using the E-test; the bacterium was sensitive to amikacin (MIC 0.75 µg/mL) and sulfamethoxazole/trimethoprim (SMZ-TMP) (MIC 0.094 µg/mL) but resistant to ciprofloxacin (MIC > 32 µg/mL). We prescribed topical amikacin (10 mg/mL), a subconjunctival injection of amikacin (50 mg/mL, 0.5 mL), and oral SMZ-TMP (800 mg/160 mg) twice daily. After 20 days on the topical and oral medications, and after three subconjunctival injections of amikacin, moderate improvement was evident. Then, based on recent studies, the patient was commenced on oral ciprofloxacin (500 mg twice daily) despite the drug-resistance evident *in vitro*.^{2,3,8} After significant improvement of the symptoms and signs of scleral infection 10 days later, oral prednisone (60 mg/day) and topical prednisolone acetate (0.12% w/v) were commenced. Forty-five days later, the scleritis was eliminated, based on resolution of scleral ulceration, lack of redness, and no subjective pain. An area of scleral thinning (from 2 to 8 o'clock) remained. Two months later, the patient was fully recovered and his visual acuity was 20/25 (Fig. 1 c,d).

3. Materials and methods

3.1. Medical record review

We retrospectively describe a patient with culture-proven nocardial scleritis.

3.2. Literature search

We retrieved all articles and case reports published from 1900 to 2015 using the terms nocardia/nocardial scleritis or sclerokeratitis. We searched PubMed (National Library of Medicine), Scielo (Scientific Electronic Library Online), and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde). Studies were considered eligible if they were human cases of culture-proven nocardial scleritis. We excluded articles describing scleritis caused by other than *Nocardia* spp. and those lacking information on diagnosis or treatment.



Fig. 2. Microbiology of *Nocardia pseudobrasiliensis*. A. A photomicrograph (Ziehl-Neelsen staining, 1000×) showing filamentous branching rods after 3 days of incubation. B. A photograph of a Lowenstein–Jensen culture plate showing light-orange colonies. C. Photograph of a blood agar plate exhibiting colony growth. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. Algorithm for disease management

Together with our case, we found reports on 43 eyes with nocardial scleritis. Clinical features, outcomes, microbiological diagnoses, clinical management, and surgical interventions were compared to derive a flow diagram that may help ophthalmologists make informed decisions at each key interventional point.

Ethical approval

The study was approved by the Universidade Federal de São Paulo Ethics Committee (reference 55739216.9.0000.5505).

4. Results

The 43 case reports described nocardial scleritis in both genders (males 67%); all cases had a history of chronic ocular pain and redness for 14–70 days prior to visiting an ophthalmologist. Other symptoms were blurred vision (20%), photophobia (7%), tearing (4%), and mucous discharge (4%).

Clinically, nodular, multifocal scleral abscesses predominated (32%),^{1,3,6,8,10,15,20,22} followed by ulcerative scleritis^{1,7,13,18,19,21,23,24} and combinations thereof.^{1,3,12,16,17,25} Four studies reported keratitis^{1,2,7,14}; one patient wore a soft contact lens.¹⁴ The predisposing factors were, in decreasing order: prior ocular trauma (21/43), prior surgery (17/43), the use of steroids (7/43), and a previous corneal infection (2/43). A single case report suggested the following predisposing factors: diabetes mellitus,¹³ subtenon steroid administration,²⁴ pterygial surgery,²⁶ and prior penetrating keratoplasty.¹⁷ Nocardial scleritis could occur in the absence of prior ocular surgery or trauma and could mimic immunological necrotizing scleritis.^{1,22}

The most common nocardial agent was *N. asteroides*.^{1,3,6,12-21,23-26} Of six patients with serious complications, such as scleral thinning,^{3,6,17,18} endophthalmitis,⁶ and enucleation,²³ all were infected with *N. asteroides*.^{1,3,6,17,18,23} The prognosis of resolution was fair (83%) if treatment commenced early.^{1-3,7,8,10,12,14,19-22,24-26}

Gram-staining was the most common diagnostic modality, revealing Gram-positive, thin, branching beaded rods.^{1,3,6,7,10,12,13,17-20,22-26} *Nocardia* was weakly positive on acid-fast staining (1%, w/v) and thin branching rods were evident on Ziehl-Neelsen staining.^{1,3,7,10,22,25} About 20% of cases were negative on acid-fast staining.^{1,16,17} All studies reported that slow-growing, small, dry colonies varying in terms of pigmentation grew on agar plates, but most bacteria did not grow on blood chocolate^{3,7} or Sabouraud agar.^{3,15,17,20}

Phenotypic identification of *Nocardia* was achieved (to some extent) biochemically (urease production, an inability to hydrolyze casein, xanthine and tyrosine production, and an inability to grow on 0.4% [w/v] gelatin).^{3,16,25} Diagnoses were achieved in five studies (including our present study) using PCR and sequencing.^{1,7,10} Amikacin was the preferred topical antibiotic; most bacteria were susceptible *in vitro*.¹ One study described resistance to amikacin but susceptibility to cephalosporin.¹⁶ Some studies combined amikacin with topical cephalosporin or quinolone, with good results.^{1,3,8,16,22} Only one study reported a complication associated with amikacin use. Knox¹⁹ described a corneal epithelial defect developing 1 week after prescription of amikacin (3.4 mg/mL) eyedrops, but usage frequency was not reported, and sodium sulfacetamide (30% w/v) eyedrops had also been used on an hourly basis.

All eyes treated with topical SMZ-TMP showed evidence of scleral thinning.^{17,23,24} However, SMZ-TMP was the predominant oral antibiotic employed, although only a few studies featured susceptibility testing.^{1-3,7,8,10,12-14,17-21} Oral linezolid (600 mg 12/12 h)^{27, 42,44} was considered the next best alternative.²⁶ If both SMZ/TMP and linezolid resistance were evident, the use of imipenem was suggested.²⁶

Other systemic options included fluoroquinolones (ciprofloxacin 500 mg, 12/12 h),^{2,4,31} or both gatifloxacin (400 mg 12/12 h³⁴) and

minocycline (100–200 mg, 12/12 h).^{3,11,21,45} Topical options included cefazolin (50 mg/mL 1/1 h),^{2,11,14} fluoroquinolones 1/1 h (gatifloxacin 0.3% w/v³¹; moxifloxacin 0.5% w/v;³⁴ or ciprofloxacin 0.3% w/v^{2,4}), polyhexamethylene biguanide (0.02% w/v 1/1 h),¹⁹ and polyvinyl alcohol iodine (0.033% w/v 4 ×/day).²⁰ Topical amikacin was sometimes given in combination with imipenem (5 mg/mL),²⁷ clotrimazole,²⁰ and sodium sulfacetamide (30% w/v, 1/1 h).^{15,22}

Of all 43 cases, 75% underwent surgical debridement. Of the 11 cases reported by DeCroos, all required surgery.¹

5. Discussion

Diagnosis of nocardial scleritis is difficult because of the absence of any pathognomonic epidemiological data, symptoms, signs, or microbiological tests.^{1,4,10} Therefore, detailed knowledge of the clinical features and the possibilities of misdiagnosis are essential. It is important to consider nocardiosis in cases of unilateral anterior scleritis or sclerokeratitis, combined with a trauma history involving organic materials or recent ophthalmic surgery. However, nocardiosis may occur in the absence of any predisposing factor.²² In our case, the patient denied any recent injury but his work as a homebuilder potentially exposed him to ocular trauma in habitats favored by *Nocardia* spp.

Important differential diagnoses include other inflammatory/infectious disorders of the anterior segment of the eye, especially infections with other aerobic *Actinomycetales* such as non-tuberculous *Mycobacterium*, *Corynebacterium*, *Gordonia*, *Rhodococcus*, and *Tsukamurella*.^{2,4} It is also important to differentiate nocardiosis from fungal infections, as the initial presentation and risk factors are similar. Other differential diagnoses are systemic autoimmune diseases, especially rheumatoid arthritis.²³ Systemic laboratory blood tests are required, as are chest X-rays, the tuberculin test, ultrasonography to exclude posterior scleritis, direct smears, and culture.^{2,4,22}

The clinical presentation of nocardial scleritis is principally chronic diffuse scleritis with nodules and/or necrotic abscesses.^{3,6,8,10,15,20,22} Although nocardial scleritis is believed to reflect the extension of a corneal infection to the limbus,^{3,10,17,22,26} only 6 of the 43 cases described involvement of the limbus or cornea; we thus speculate that the sclera may also be the primary site of nocardiosis.^{1,7,14}

In microbiological terms, it is always prudent to perform smears and schedule cultures, even when a nocardial etiology is strongly suspected. The most common nocardial species involved in scleritis is *N. asteroides*,^{1,3,6,12-21,23-26} but polymicrobial infections can also occur, requiring appropriate treatment.¹ In natural environments, *Nocardia* typically occurs with many other types of bacteria.^{2,3}

Gram-staining is of low specificity; false-negatives are possible when Ziehl–Neelsen staining reveals only weakly acid-fast organisms because *Nocardia* grows slowly on most media.³ It is important to evaluate growth on Lowenstein–Jensen agar; although this does not differentiate *Nocardia* from *Mycobacterium* species, nocardial growth is rapid, accompanied by characteristic light-orange pigmentation.^{7,15}

Sophisticated PCR tests can be used to identify pathogens to the species level and they yield data on antibiotic susceptibility.^{5,11,28} In clinical practice, 16S rRNA gene sequencing is often not available, so effective empirical therapy is essential. Treatment must include topical and oral medications and surgical debridement; rapid complete resolution is possible (Fig. 3). Topical amikacin (5% w/v) is most commonly used, affording a high success rate when combined with oral SMZ-TMP (800 mg/160 mg) every 12 h.

Penetration of topical drugs is poor. Scleral tissue is avascular and contains many collagenous fibers. Microorganisms may persist for a long time in the intra-scleral lamellae.⁹ Thus, treatment is long, tedious, and requires early (and possibly repeat) debridement.⁹

6. Conclusions

It is important to consider nocardiosis in every patient with scleritis

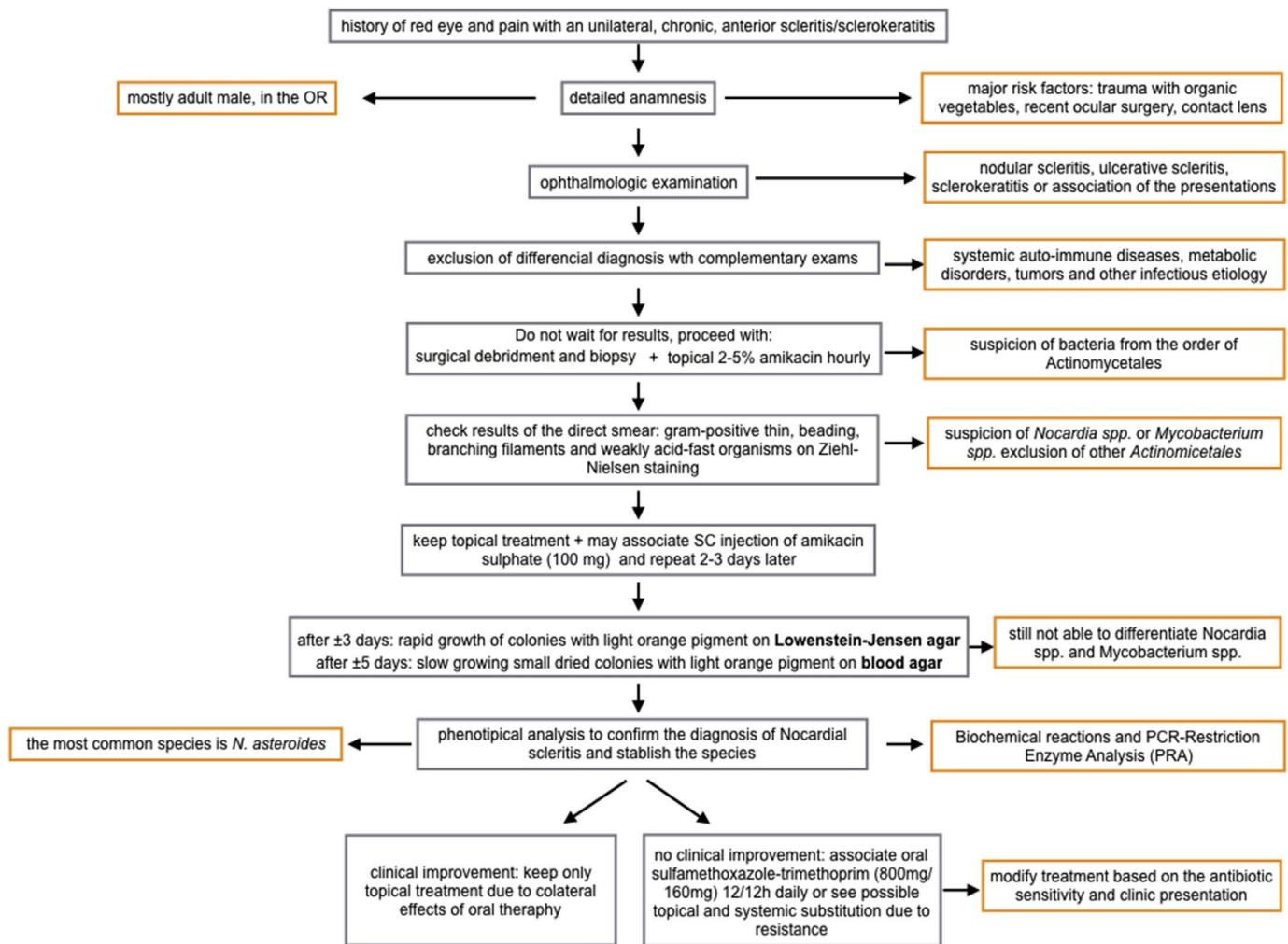


Fig. 3. The Nocardial Scleritis Clinical Algorithm: from clinical presentation to diagnosis and management.

or sclerokeratitis and a trauma history involving organic materials or recent ophthalmic surgery.^{4,5,17} No stain is specific for *Nocardia* and the bacterium grows slowly in most media, delaying diagnosis, the commencement of specific treatment, and/or creating a false-negative culture result.² Mass spectrometry (MALDI-TOF) technology is diagnostic, but PCR is generally required to successfully identify the bacterium to the species level and provide antibiotic-susceptibility information.^{11,28}

Treatment is long and may feature early (and possibly repeat) debridement associated with topical and oral medications.⁹ Amikacin (5% w/v) was the most commonly used topical drug, and was very successful. If amikacin resistance is evident, several options such as linezolid are available, but drug choice must be based on antibiotic-susceptibility testing.^{2,29,30} In terms of systemic treatment, the best option is oral SMZ-TMP.^{2,7,8,13,14,17-21}

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