**Nocardia asteroides** keratitis

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**SUMMARY** *Nocardia asteroides* has been reported as the cause of keratitis in only 7 cases and of other ocular disease in another 12 cases. We report a case of *N. asteroides* keratitis that presented 3 weeks after rural trauma and progressed despite trials of appropriate antibiotics. Seven weeks after the original injury a successful conjunctival flap was placed over the cornea. The morphology and the sensitivity testing of *N. asteroides* with agar dilution methods are described. Further standardisation of susceptibility testing of *N. asteroides* to antibiotics appears necessary before reliable information can be obtained for clinical use. Moreover, our case did not show the relatively benign course of other reported cases of nocardia keratitis.

Although fungal keratitis has been reported more often since the introduction of topical ocular steroid preparations (Haggerty and Zimmerman, 1958) there have been only 7 reports of *Nocardia asteroides* as the causative organism. A further 13 cases (3 bilateral) of ocular or periocular infection with this organism have also been reported.

We report a case of a progressive *N. asteroides* corneal ulcer that was unresponsive to intensive oral and topical antibiotics. One year after a Gundersen conjunctival-flap operation the eye is quiet, and a potentially useful eye has been retained.

**Case report**

**CLINICAL SUMMARY**

A 17-year-old Caucasian boy sustained injury from foreign bodies in both corneas when dirt and debris from an exploding tractor tyre peppered his eyes. He had numerous foreign bodies removed from both eyes on the day of the accident and on the following day, and received topical sulphadiazine drops. His vision and comfort gradually improved over the ensuing 3 weeks, after which his left eye became painful and visual acuity progressively diminished. He was admitted to a local hospital and given sodium sulphacetamide eyedrops for 1 week without improvement. When seen at the Johns Hopkins Hospital about 1 month after the initial injury his right eye had 20/20 vision. There was a half-thickness healed corneal laceration inferonasally, with few foreign bodies trapped within the scar. His left eye was rather photophobic and had gross conjunctival chemosis and ciliary injection. There was a 5 × 5 mm one-third-thickness stromal ulcer inferonasally with irregular opaque edges (Fig. 1). Feathery projections from these edges extended for a further 1 to 2 mm at mid-stromal depth and there was a mid-stromal ‘satellite’ infiltrate 2 mm above the ulcer. The base of the ulcer was irregular and filled with mucus and corneal debris. The pupil was mid-dilated, and there was an intense fibrinous exudate in the anterior chamber. The lens, vitreous, and retina were normal. Vision

**Fig. 1** *Nocardia asteroides ulcer on initial presentation at the Johns Hopkins Hospital, 4 weeks after trauma*
was reduced to counting fingers at 3 ft (1 m).

Before the accident the patient had been in good health and had 20/20 vision, with surgery at the age of 3 for correction of strabismus. He had been on long-term tetracycline therapy for acne before this eye infection, but he ceased this medication on his first hospital admission after the infection. He gave a reliable history of penicillin allergy.

Smears and cultures taken on his initial admission to the community hospital were reported a week later as positive for Nocardia asteroides and Alcaligenes species. At the Johns Hopkins Hospital, 28 days later, the corneal ulcer was again scraped for smears and cultures and the patient was begun on sulphadiazine orally, 2 g every 6 hours, 30% sulphacetamide drops every 2 hours, 3% atropine drops 3 times a day, achromycin drops every 2 hours, and gentamicin drops every 2 hours. Smears taken from corneal scrapings confirmed the presence of partially acid-fast Gram-positive organisms with branching hyphae, and after 2 days cultures confirmed the presence of N. asteroides. Other cytological examinations were normal except for neutrophilia.

One week later the lesion and the surrounding infiltrate and anterior-chamber reaction had increased slightly. The ulcer was again scraped. No organisms were noted on smear, but cultures again grew N. asteroides.

Six weeks after the initial injury, despite daily irrigation of the ulcer and continuation of the intensive antibiotics, an endothelial line of keratic precipitates developed around the ulcer. This line and the ulcer size and depth showed progression over the next 2 days. A hypopyon formed, and the endothelial line extended towards the limbus (Fig. 2). Topical antibiotics were discontinued and subconjunctival gentamicin was begun, with continuation of the oral sulphadiazine.

Over the next 5 days the ulcerated cornea thinned to less than one-quarter thickness, and the anterior-chamber reaction increased. A further scraping was performed, but no organisms were seen on smear. A conjunctival flap was placed over the entire cornea, and the eye soon became quiet. The oral sulphadiazine was continued for 2 months. One year later, the conjunctival flap had thinned and the anterior chamber, lens, and retina (posterior pole only) were visualised as normal. The intraocular pressure as measured by pneumotonometry was 15 mmHg. The nasal half of the cornea was thinned to half-thickness over an area of 5 × 4 mm (Fig. 3). The cornea in this area was opaque, but the eye was quiet, and the uncorrected vision was 20/200. Later a 7-mm penetrating keratoplasty was successfully performed, and no organisms were found on histological examination of the corneal specimen.

**Microbiological Examination**

Corneal scrapings submitted soon after the patient was admitted to the Johns Hopkins Hospital revealed an aerobic growth of a pure culture of small, white, raised, dry colonies. Gram staining showed Gram-positive branching pleomorphic rods. Acid-fast staining by the Ziehl-Neelsen technique with a 3% HCl-ENH decolorisation for 10 seconds showed partially acid-fast organisms. Biochemical testing revealed no acid production from lactose and xylose, urea was decomposed but tyrosine and xanthine were not, and there was no casein hydrolysis. The organism was identified as Nocardia asteroides. Subsequent specimens from the corneal ulcer submitted 7 days later grew the same organisms
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in pure culture. Susceptibility testing of the organisms cultured at the Johns Hopkins Hospital was done by an agar dilution technique as follows. The inoculum was prepared by incubating the organism in Mueller Hinton broth for 24 hours at 35°C. After vigorous vortexing, the larger particles were allowed to settle, and the suspension was removed and standardized against a 0.5 MacFarland BaSO₄ standard. This suspension was diluted 1:10 and 0.01 ml was applied to the surface of the antibiotic-containing Mueller Hinton agar by means of a replicating device. All plates were incubated at 35°C for 48 hours before being examined. Inhibition was defined as no growth, 3 or fewer colonies, or the presence of a slight haze.

The minimal inhibitory concentration (MIC) results of the antibiotics tested were as follows: methicillin, greater than 16 μg/ml; penicillin, 16 μg/ml; erythromycin, greater than 2 μg/ml; clindamycin, 2 μg/ml; tetracycline, 16 μg/ml; chloramphenicol, greater than 8 μg/ml; cephalothin, greater than 32 μg/ml; ampicillin, 2 μg/ml; gentamicin, greater than 1 μg/ml.

Discussion

Nocardia are usually soil organisms, and, although they are worldwide in distribution, nocardial infections are rare, especially in the eye. The 2 most usual modes of infection are inhalation of organisms, leading to pulmonary nocardiosis; and contamination of skin wounds with soil, leading to chronic destructive mycetomas. Nocardia asteroides is usually an opportunistic pathogen, and pulmonary or generalised nocardiosis has become increasingly prevalent in patients with severe systemic diseases who are receiving corticosteroids or antineoplastic drugs. In addition, nocardia may rarely cause infections in other sites.

The Nocardia genus and the genus Actinomyces are members of the family Actinomycetaceae. Both genera grow as fragile branching filaments that readily fragment into bacillary rod and twig-like elements. Nocardia are aerobic and somewhat acid-fast, whereas Actinomyces are anaerobic and not acid-fast. With their filamentous growth and mycelia-like colonies, the actinomycetes have a striking resemblance to fungi. However, a number of basic biological properties establish them as bacteria (Davis et al., 1969; Bach, 1975). Occasionally confusion arises in differentiating Nocardia from rapidly growing mycobacteria. Similarity between the genus Mycobacterium and the genus Nocardia has also been reported with respect to antigenic structure, cell-wall composition, and bacteriophage susceptibility. Nocardia, however, may be differentiated from mycobacteria because Nocardia is only partially acid-fast, it forms fragmenting mycelia and has true branching (Tsukamura, 1970). In addition, the 2 groups differ in the lipid composition of their cell walls (Davis et al., 1969; Lechevalier et al., 1971).

Nocardia is commonly involved in pulmonary infections, but its role in ocular infections is limited, as is evident from a search of the available literature (Table 1) (Bruce and Locatcher-Khorazo, 1942; Benedict and Iverson, 1944; Smith, 1952; Schadt et al., 1956; Sigtenhorst and Gingrich, 1957; Henderson et al., 1960; Gingrich, 1962; Rees, 1962; Davidson and Foerster, 1967; Meyer et al., 1970; Burpee and Starke, 1971; Newmark et al., 1971; Panjayanond et al., 1972; Jampol et al., 1973; Rogers and Johnson, 1977; Sher et al., 1977). Most of the intraocular cases of nocardia infection can be traced to metastatic spread of proved primary infections elsewhere, (Davidson and Foerster, 1967; Meyer et al., 1970; Burpee and Starke, 1971; Panjayanond et al., 1972, Jampol et al., 1973; Rogers and Johnson, 1977; Sher et al., 1977) or following exogenous trauma such as cataract extraction (Meyer et al., 1970). Five of the 7 previously reported nocardia infections of the cornea were preceded by trauma; 4 of these occurred in a rural setting (Schadt et al., 1956; Sigtenhorst and Gingrich, 1957; Gingrich, 1962; Newmark et al., 1971), and 1 was from a fishing accident (Ralph et al., 1976). The trauma in all cases was considered trivial. The cases ran variable courses, but all resolved with retention of the eye and with reasonably good vision. The remaining 2 cases were associated with a keratoconjunctivitis of obscure origin (Bruce and Locatcher-Khorazo, 1942; Benedict and Iverson, 1944). One of the cases responded to therapy, but the other was deteriorating when lost to follow-up.

In only 3 of the 7 cases was the topical administration of corticosteroids (Sigtenhorst and Gingrich, 1957; Newmark et al., 1971; Ralph et al., 1976) a possible predisposing factor, and in these cases the drugs had been administered only briefly before the diagnosis of nocardial infection. These patients retained excellent vision. Often, however, the isolation of the causative organism may be delayed, and steroids may have been given for several months.

Our case emphasises the rural trauma, the slow initial course of the disease, the characteristic morphology of a ‘fungal-type’ ulcer, and the progressive nature of a nocardial infection when it is unresponsive to treatment. In this case intensive sulphonamide therapy, topically and systemically, was given in conjunction with tetracycline and gentamicin. Daily toilet of the ulcer, and 3 of the
Table 1  Review of literature on ocular nocardiosis

<table>
<thead>
<tr>
<th>Case report</th>
<th>Age</th>
<th>Sex</th>
<th>Predisposing cause</th>
<th>Site of infection</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce and Locatcher-Khorazo (1942)</td>
<td>50</td>
<td>M</td>
<td></td>
<td>Punctate keratoconjunctivitis</td>
<td>Potassium iodide (a, b)</td>
<td>Quiet eye</td>
<td></td>
</tr>
<tr>
<td>Benedict and Iverson (1944)</td>
<td>23</td>
<td>F</td>
<td>? Scarlet fever</td>
<td>Chronic keratoconjunctivitis</td>
<td>Sulphanilamide (a) Potassium iodide (a) Copper sulphate (a) Zinc sulphate (a) Metaphen (a) Penicillin (a)</td>
<td>4 years gradual deterioration</td>
<td>Positive smear and culture</td>
</tr>
<tr>
<td>Schardt et al. (1956)</td>
<td>33</td>
<td>M</td>
<td>Stone trauma on farm</td>
<td>Corneal ulcer</td>
<td>Argyrol (a) Cautery oxytetracline (a) Atropine (a) Achromycin (a, b)</td>
<td>20/80 quiet</td>
<td>Positive culture</td>
</tr>
<tr>
<td>Sigtenhorst and Gingrich (1957)</td>
<td>?</td>
<td></td>
<td>Cotton branch injury</td>
<td>Corneal ulcer</td>
<td>Sulphacetamide (a) Atropine (a) Cortisone (a)</td>
<td>Excellent</td>
<td></td>
</tr>
<tr>
<td>Gingrich (1962)</td>
<td>53</td>
<td>M</td>
<td>Cotton plant scratch</td>
<td>Corneal ulcer</td>
<td>Sulphacetamide (a) Penicillin (c) Sulphadiazine (b)</td>
<td>20/50</td>
<td>Positive culture</td>
</tr>
<tr>
<td>Newmark et al. (1971)</td>
<td>6</td>
<td>M</td>
<td>Dirt injury</td>
<td>Corneal ulcer</td>
<td>Oxytetracycline (a) Corticosteroid (a) Chloramphenicol (a) Sulphacetamide (a) Tetracycline (a) Iodoxuridine (a) Sulphadiazine (b)</td>
<td>20/25</td>
<td>Positive culture</td>
</tr>
<tr>
<td>Ralph et al. (1976)</td>
<td>11</td>
<td>F</td>
<td>Fishline sinker abrasion</td>
<td>Corneal ulcer</td>
<td>Neomycin (a) Prednisone (a) Homatropine (a) Polyvinix (a) Gentamicin (a) Erythromycin (a) Ampicillin (d) Sulphacetamide (a) Penicillin (a) Bacitracin (a)</td>
<td></td>
<td>Positive culture</td>
</tr>
</tbody>
</table>

*Route of administration: a, topical; b, systemic oral; c, systemic parenteral; d, periorcular; e, intraocular

scrapings during the early course of the infection, always revealed only the presence of nocardia. The initial growth of alcaligenes was not observed on subsequent scrapings. Although it is not at all certain that long-term use of a broad-spectrum antibiotic contributed to a predisposing state, it is interesting to note that the patient was on continuous oral tetracycline therapy for acne at the time of his injury and subsequent infection, until he discontinued the tetracycline when he first entered the hospital. In-vitro testing revealed resistance of the nocardia to tetracycline.

In the face of progressive corneal thinning and increased anterior-chamber reaction despite a 3-week period of intensive chemotherapy, an operation for conjunctival flap was performed, and the oral sulphadiazine was continued for 2 months postoperatively. Therefore the dramatic response after surgery is more difficult to evaluate; it could have been due to the prolonged chemotherapy, but the lack of favourable response to sulphadiazine preoperatively makes this unlikely.

Sulphonamides, both systemic and topical, have remained the drugs of choice for ocular nocardia infections (Lerner and Baum, 1973; Ripon, 1974). Sulphadiazine and sulphamethoxazole still appear to be superior to newer antimicrobial agents for treatment of nocardiosis (Black and McNellis, 1971; Ripon, 1974). Cephalexiride and also a trimethoprim-sulphamethoxazole combination have both been used successfully in systemic nocardiosis (Baikie et al., 1970; Lerner and Baum, 1973; Maderazo and Quintiliani, 1974; Ripon, 1974). With the nocardia recovered in the present case, however, susceptibility testing against other antimicrobials was done by agar dilution, and the results were as reported above.

There are many reports of antibiotic susceptibility
of nocardia (Black and McNellis, 1971; Bach et al., 1973; Lerner and Baum, 1973). It is difficult to compare the results of our single strain of nocardia with those in the literature, since different strains vary in susceptibility. There are numerous problems and variations inherent in the testing (Lerner and Baum, 1973; Bach, 1975). However, our method of susceptibility testing, which closely follows the method of Wallace et al. (1977), produced results similar to theirs.
Because nocardia tends to grow in clumps it is difficult to prepare uniform and reproducible suspensions containing equivalent numbers of organisms. In addition, in-vitro susceptibility is influenced by pH and type of agar used in the assay. Variation in these parameters may well explain conflicts in results of susceptibility testing reported in the past. Further, in-vitro susceptibility may not correlate well with clinical response (Black and McNellis, 1971; Bach et al., 1973; Lerner and Baum, 1973; Lennette et al., 1974). For example, cyclomycin or even the sulphonamides may appear ineffective by in-vitro testing despite a good clinical response.

After the present case 2 further isolates of Nocardia asteroides were obtained from 2 other patients with non-ocular nocardiosis. Antimicrobial susceptibility testing was performed as before. Marked differences from the present results were obtained with some of the antibiotics. We can conclude that susceptibility testing will continue to be difficult to evaluate until standardised methods of testing for this species are established.

The favourable long-term result in this case appears to have been achieved by covering the cornea with a conjunctival flap, followed by penetrating keratoplasty 24 months later.

References


