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Severe Keratitis Due to *Nocardia farcinica*

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Keratitis due to *Nocardia farcinica* occurred in a 49-year-old female after inappropriate cleaning of her semipermeable rigid contact lenses with basin-stored water during a holiday in France. *N. farcinica* was differentiated from *Nocardia asteroides* by its growth at 45°C, acid production from rhamnose, its opacification of Middlebrook 7H10 agar, and its marked degree of resistance to all cephalosporins, aminoglycosides, tetracyclins, macrolides, and trimethoprim-sulfamethoxazole. To the best of our knowledge, this is the first reported case of human *N. farcinica* keratitis, confirming that this microorganism can be responsible for serious human disease.

Nocardiosis is an infection caused by several species of the genus *Nocardia*. *N. asteroides* and *N. brasiliensis* are the two most frequently encountered pathogens responsible for systemic life-threatening and localized infections (2, 13, 19). The eye can be infected at different sites, giving rise to endophthalmitis (12), scleritis (11), or keratitis (3-5, 9, 17, 18, 23). *Nocardia* spp. are typically soil saprophytes and frequently cause systemic infections in immunocompromised hosts. Local traumatic inoculation of the eye also causes a severe keratitis, especially if the organism is not recognized or is mistaken for nonpathogenic diphtheroids.

Herein, we describe a case of keratitis caused by *Nocardia farcinica* in a patient who, in exception to normal practice, cleaned her semipermeable rigid contact lenses with basin-stored water. Thus far, only 15 cases of human infection due to this microorganism have been described, with none of them affecting the eye (10, 20, 24).

A 49-year-old female was referred to our hospital in September 1995 with a slowly progressing keratitis of the left eye. She had been treated sequentially with locally applied antibiotics (cephazoline, fusidic acid, chloramphenicol, and tobramycin), acyclovir ointment (3%), and corticosteroids in the previous 6 weeks by three different ophthalmologists. The infection started during a camping vacation in France in August 1995 when she cleaned her semipermeable rigid contact lenses in basin-stored, unchlorinated rainwater. Two weeks thereafter, her vision became clouded and she consulted an ophthalmologist. The patient presented with a painful red left eye, and her visual acuity was limited to counting fingers at a distance of 1 m. The inflamed eye showed a multilobulated, punched-out lesion in the cornea, with three centrally located infiltrates (Fig. 1). Corneal sensitivity was diminished compared to that of the contralateral eye. The anterior chamber was only slightly inflamed. Although the clinical aspect at first inspection was not typical for an *Acanthamoeba* infection (22), this was a strong consideration in the differential diagnosis because of continued inflammation after topically applied antibiotics and antiviral agents and because of the slowly progressive course. Corneal scrapings were taken and used to prepare slides for

Gram and Giemsa staining and to inoculate nonnutrient agar plates (1.5% agar in distilled water overlaid with *Escherichia coli*), blood agar, chocolate agar, Sabouraud glucose agar (2%), and supplemented Peptone Broth II (Becton Dickinson, Cockeysville, Md.) for culturing. A swab was immediately transported to the virology laboratory and was inoculated into cell cultures. Microscopical examination of the Gram-stained slides revealed no bacteria, but the Giemsa-stained slides showed one cyst-like structure suspected of being *Acanthamoeba*. Local therapy consisting of polyhexamethylene biguanide (0.02%), propamidine isethionate (0.1%), and neomycin (0.5%) was started. Cultures for *Acanthamoeba*, herpes simplex virus, and fungi remained negative. The bacterial cultures grew few gram-positive diphtheroids which were not further identified. After 6 weeks of topical therapy for a suspected *Acanthamoeba* infection, no clinical improvement was observed and repeated cultures (only swabs) showed no growth. The diphtheroids previously cultured were not detected. The same locally applied therapy was continued until December 1995, when a yellow infiltrate in the limbal region developed. At this point, a biopsy of the corneal infiltrate was obtained for direct microscopy, culture, and histopathology. Direct Gram staining showed beaded gram-positive branched filamentous bacteria, and a modified Kinyoun staining that employed 1% H₂SO₄ as a decolorizer showed the bacteria to be acid fast, which are results suggestive of a *Nocardia* species. The organism was presumptively identified as *Nocardia asteroides* based on its failure to hydrolyze casein, xanthine, hypoxanthine, and tyrosine. Histopathology demonstrated a severe necrotizing keratitis with branched gram-positive microorganisms. No cysts suggestive of *Acanthamoeba* were observed.

Based on the direct Gram staining, the treatment was changed to topical therapy with sulfacetamide (10%) and amikacin (13 mg/ml) combined with oral trimethoprim-sulfamethoxazole (960 mg twice daily), which was changed after 5 days to doxycycline (200 mg twice daily) because of a hypersensitivity reaction. A slow recovery was observed over a 2-month-period during which the local therapy was continued. Eight months after the cessation of the antimicrobial therapy, the cornea was still very cloudy due to scarring and, therefore, a therapeutic penetrating corneal transplantation was performed. Cultures of the removed cornea remained culture negative, and histologically no microorganisms were observed.

The results prompted us to reexamine the presumed *Corynebacterium* species recovered from the first scrapings in Septem-

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FIG. 1. Multilobulated greyish corneal ulcer, centrally located on the cornea, with three distinct whitish infiltrates.

ber 1995, which also appeared to be a *Nocardia* species after Kinyoun staining. The isolates were submitted to the French National Reference Center for Human Mycoses and Antifungal Agents in Paris, France, for further evaluation and susceptibility testing.

Microbiology. The isolates were filamentous, gram positive, and partly acid fast. After 72 h of aerobic incubation, small, orange-pigmented colonies were identified on the plates. The pigment was not diffusible. No aerial hyphae were present. Vegetative hyphae were branched, fragmenting into bacteroid to coccoid elements. Thin-layer chromatography showed that the isolate contained the mesoisomer of diaminopimelic acid, as well as galactose, arabinose, and nocardiomycolic acids (15, 16, 21). The isolate failed to hydrolyze casein, xanthine, hypoxanthine, tyrosine, adenine, uric acid, and Tween 20; it did hydrolyze esculin (7) and urea (Christensen urea agar; Sanofi Diagnostics Pasteur, Marnes la Coquette, France). Identification of *N. farcinica* was proven by equivalent growth at 45 and 35°C (25), the production of acid from rhamnose (25), and opacification of Middlebrook 7H10 agar supplemented with oleic acid, albumin, dextrose, and catalase (Difco, Detroit, Mich.) (6). Antibiotic resistance was determined by disk diffusion on Mueller-Hinton agar (Biomerieux, Marcy l'Etoile, France) after 24 to 36 h of incubation at 37°C (1) and was found to be compatible with *N. farcinica* (25). Both strains had in vitro susceptibility to imipenem and amikacin and were resistant to cephalothin, cefoxitin, cefamandole, cefotaxime, ceftriaxone, tetracycline, minocyclin, doxycyclin, kanamycin, tobramycin, gentamicin, chloramphenicol, erythromycin, and trimethoprim-sulfamethoxazole. The results obtained with the last drug are different from a previous report (25). This discrepancy might be explained by differences in the methods used. However, differences in the geographical origins of isolates could also be responsible for the discrepancy.

Ocular nocardiosis is a rare infectious disease which can be

seen as a spectrum of infections such as scleritis (11), endophthalmitis (12), and keratitis (3-5, 9, 17, 18, 23). Corneal infection is most frequently caused by trauma in a rural environment (4). Approximately 22 cases of corneal ulceration are described in the world literature, with two cases associated with extended wear of soft contact lenses (5, 17). Except for one infection due to *N. brasiliensis* (23) and one reportedly due to *N. gypsoides* (14), a species which is considered a variety of *N. asteroides* (8), all others have been apparently due to *N. asteroides*, although no one has specifically looked for *N. farcinica*. In contrast, our patient presented with an *N. farcinica* keratitis associated with rigid contact lenses.

Many clinical microbiology laboratories use the hydrolyzation patterns of casein, hypoxanthine, xanthine, and tyrosine for identification of the human-pathogenic *Nocardia* species. By using this scheme, only the *N. asteroides* complex, *N. brasiliensis*, and *N. otitidiscaviarum* can be differentiated; however, as demonstrated in our case, *N. farcinica* will not be recognized. This means that in the past, cases of *N. farcinica* keratitis might have been missed due to incorrect identification. Recently, it was shown that *N. farcinica* misidentification occurred in about 20% of strains collected in a reference center, indicating that human infection due to *N. farcinica* occurs more frequently than previously recognized (25). *N. farcinica*, which was originally isolated by Nocard from a case of bovine farcy, is the classical cause of bovine nocardiosis. The idea of occurrence of human nocardiosis due to *N. farcinica* has been controversial in the last 2 decades. In recent years this species, which shows in vitro resistance to many antimicrobial agents, has been implicated several times in human infections (10, 19, 20, 24, 25).

Keratitis due to *Nocardia* spp. runs a slowly progressive course and initially shows a granular appearance with an epithelial defect with scalloped margins, progressing to ulceration with moderate stromal loss (18). It can mimic a fungal or

herpetic keratitis. In cases in which contact lenses have been worn, *Acanthamoeba* should be considered too. This infection is frequently worsened by local treatment with corticosteroids (4), as was seen in our patient. The correct diagnosis of ocular nocardiosis is often delayed, because ophthalmologists tend to start empirical local antibiotics without obtaining material for diagnostic purposes. Even when diagnostic material is obtained, the clinical microbiological laboratory may fail to give a correct diagnosis due to misinterpretation of culture results as contaminating flora, as was done in our case. Furthermore, when a correct diagnosis is obtained, the differentiation of species within the *N. asteroides* complex will be poor or incomplete (25). The importance of correct identification is important for two reasons: (i) epidemiological, *N. farcinica* infections occur more frequently than previously thought and (ii) there is the potential for in vivo resistance to treatment.

The therapy of choice for *Nocardia* keratitis consists of local administration of a sulfonamide (e.g., 10 or 30% sulfacetamide) or trimethoprim-sulfamethoxazole prepared from the commercial intravenous solution (3) combined with an aminoglycoside.

In our patient, correct diagnosis was initially delayed because the cultured organisms were discarded as nonpathogenic diphtheroids and, secondly, because the finding of a single cyst-like structure in the absence of other pathogens suggested *Acanthamoeba* keratitis. Only a corneal biopsy provided adequate material to give a presumptive diagnosis, and complete identification of all isolated organisms gave the final diagnosis.

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