Combined *Phialemonium curvatum* and *Acanthamoeba* Keratitis: The Importance of Early Diagnosis and Specific Therapy

Anna M. Roszkowska, MD, PhD, Alice A. Severo, MD,* Carmelo Biondo, MD,† Elisa I. Postorino, MD, PhD,* Leandro Inferrera, MD,* and Pasquale Aragona, MD, PhD**

Purpose: To report the clinical and confocal findings of a unique case of combined *Phialemonium curvatum* and *Acanthamoeba* keratitis and to highlight the role of the prompt diagnosis and specific medical treatment in preserving visual function.

Methods: A case report and literature review.

Results: A 54-year-old woman presented with a 3-day history of visual impairment, photophobia, and ocular pain in her right eye. Her best corrected visual acuity was 0.4 Logarithm of the Minimum Angle of Resolution scale, and the slit-lamp examination showed whitish corneal stromal infiltrate with satellite lesions. In vivo confocal microscopy evidenced *Acanthamoeba* cysts and fungal hyphae that resulted *P. curvatum* in the culture examination. The intensive medical treatment was started with topical 0.02% polyhexamethylene biguanide, voriconazole 1%, and moxifloxacin hydrochloride 0.5%. Progressive improvement of clinical and confocal pictures was registered with a complete recovery of visual function after 1 month.

Conclusions: This is the first case report of combined *P. curvatum* and *Acanthamoeba* keratitis. The fast diagnosis with in vivo confocal microscopy allowed early and intensive specific treatment with recovery of corneal infection.

Key Words: Phialemonium curvatum, Acanthamoeba, keratitis, PHMB, voriconazole, in vivo confocal microscopy

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Microbial keratitis represents one of the main causes of severe visual impairment. *Acanthamoeba* keratitis is a rare condition, usually associated with contact lens wear, that is potentially devastating and requires immediate specific therapy to preserve visual function.

Phialemonium curvatum is a dematiaceous, saprobic fungus that can be isolated from soil, air, water, and sewage.[1] It is an extremely rare cause of ocular infection, with only 3 cases reported in the literature.[2,3] In all these cases, its destructive effect resulted in severe visual impairment.

Although the keratitis due to coexisting *Acanthamoeba* and filamentous fungi such as *Aspergillus* and *Fusarium* was already well documented, to date, there is no evidence reported about the associated corneal infection with *Acanthamoeba* and *P. curvatum*.

CASE REPORT

A 54-year-old healthy woman, living in a rural area, presented to our clinic with a 3-day history of intense photophobia, ocular pain, and visual impairment in her right eye. The patient reported an extended use (daytime for 12–14 h) of daily disposable silicone hydrogel contact lenses (Dailies total, Alcon, Switzerland). She also referred a frequent exposure to tap water doing shower and face cleaning with contact lenses on. No contact to organic matter nor eye trauma were reported.

Her best corrected visual acuity (BCVA) was 0.4 in Logarithm of the Minimum Angle of Resolution scale, and slit-lamp examination evidenced a paracentral corneal stromal infiltrate with a few satellite whitish lesions (Fig. 1A). In vivo confocal microscopy (IVCM) (HRT with Rostock Cornea Module, Heidelberg Engineering, GmbH, Germany) showed the presence of *Acanthamoeba* cysts (Fig. 1B) and numerous fungal hyphae (Fig. 1C) in the corneal stroma associated to inflammatory signs such as Langerhans cells (Fig. 1D), leukocytes (Fig. 1E), and stromal needle-shaped deposits (Fig. 1F).

Corneal scraping was performed and forwarded for microbiological analysis, and in the meantime, the topical treatment was started with 0.02% polyhexamethylene biguanide (PHMB) (SIFI SpA, Aci Sant'Antonio, Italy) and 1% voriconazole (hospital galenic preparation) every hour around the clock, povidone iodine solution 0.6% (Iodim MEDIVIS S.R.L., Tremestieri Etneo, Italy) 4 times daily, 0.5% moxifloxacin hydrochloride (Vigamox Alcon Italia, Milano) 6 times daily, atropine 1% twice daily, and lubricant eye drops 4 times daily (Keratostil Bruschettini Srl, Genova, Italy). Scraping material was inoculated onto the Sabouraud glucose agar and potato dextrose agar plates and incubated at 25°C. After 1 week, morphological features resembling Phialemonium species were observed on the Sabouraud plate. Identification at the species level was performed on the basis of their macro- and micromorphological features (morphology, color, size, and shape of conidia and phialides). Colonies on potato dextrose agar appeared initially flat and white, becoming greyish and smooth with time,

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From the *Department of Biomedical Sciences, Ophthalmology Clinic, University of Messina, Messina, Italy; and †Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy.

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Correspondence: Anna M. Roszkowska, MD, PhD. Ophthalmology Clinic, Department of Biomedical Sciences, University of Messina, Viale Consolare Valeria, Messina 98125, Italy (e-mail: aroszkowska@unime.it).

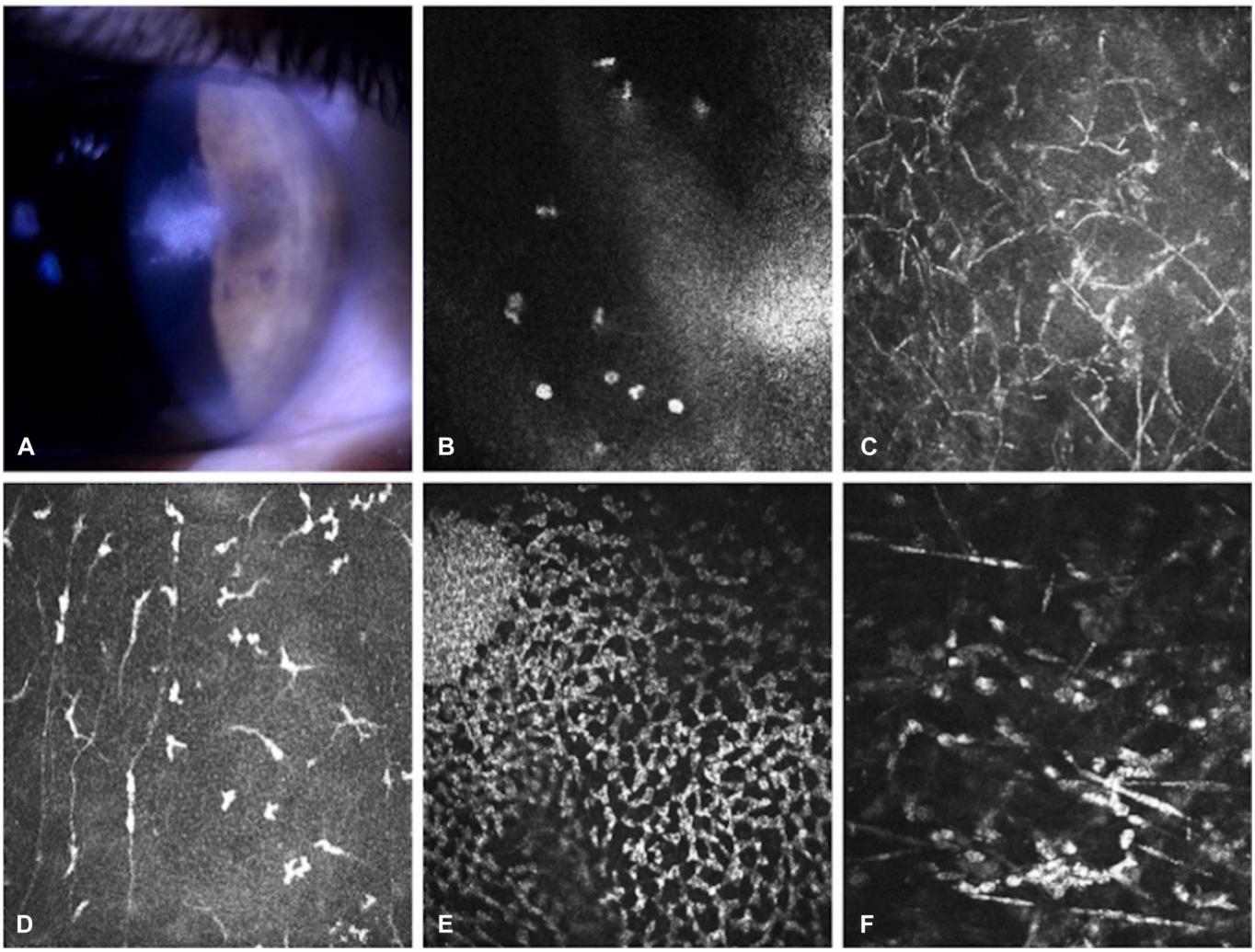

FIGURE 1. Slit-lamp and IVCM (400 × 400 μm) findings at baseline: (A) Paracentral corneal stromal infiltrate, (B) *Acanthamoeba* cysts in deep stroma, (C) fungal hyphae and *Acanthamoeba* cysts, (D) subbasal nerve fibers and Langerhans cells, (E) leucocytes, and (F) stromal, needle-shaped structures and activated keratocytes. (The full color version of this figure is available at www.corneajrnl.com.)

reaching 45 mm in 14 days at 25°C. Microscopic observation showed unicellular conidia, smooth and thin-walled, hyaline, cylindrical, and allantoid with dimensions of 3.5 to 6.2 × 1.1 to 1.6 mm, aggregating in slimy heads. Conidia were produced from abundant adelophialides that, unlike common phialides, are often without basal septa. Chlamydospores were not observed. Based on these features, the isolate was morphologically identified as *P. curvatum*.

Acanthamoeba was not identified on the culture, and the stain was not performed. We based the diagnosis on typical clinical and IVCM findings.

At 1-week control, clinical improvement was registered with reduction of stromal infiltrate, and fewer hyphae and cysts on IVCM examination. The therapy continued with 1% voriconazole and 0.02% PHMB every hour during the day for 1 week and successively 6 times daily for a month; povidone iodine continued 4 times daily for a month; moxifloxacin hydrochloride was continued 5 times daily, and lubricant eye drops 4 times daily for the other month; atropine eye drops were suspended. One month later, a further improvement of clinical and IVCM conditions were observed, with a BCVA of 0.0. The moxifloxacin and voriconazole drops were gradually tapered to 4 times daily and suspended after a further 1 month; povidone iodine administration was reduced to 2 times daily for 2 weeks and stopped, whereas the PHMB was continued for 6 months 4 times daily. No steroids were used during the whole treatment. After 6 months, the cornea appeared transparent with a localized paracentral, translucid scar (Fig. 2A) and a BCVA of 0.0 as measured with a Logarithm of the Minimum Angle of Resolution scale.

At IVCM, *Acanthamoeba* cysts and fungal hyphae were absent; furthermore, no inflammatory cells were observed; however, a reduced number of stromal needle-shaped structures were still present (Figs. 2B–D).

DISCUSSION

Microbial keratitis can be considered an ophthalmic emergency that requires immediate diagnosis and treatment. If untreated, or inappropriately treated, it can lead to corneal perforation with a risk of endophthalmitis. The early

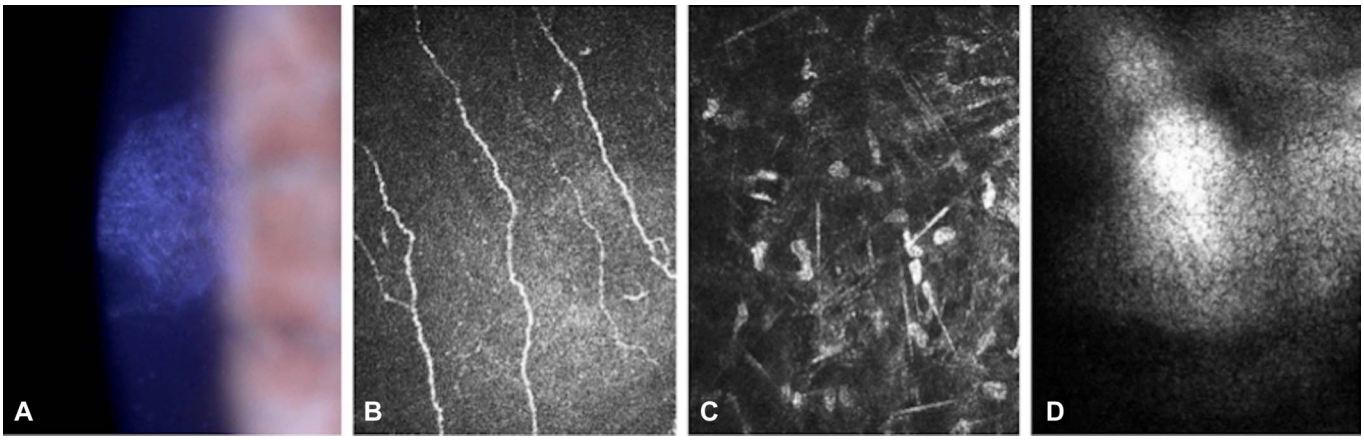

FIGURE 2. Slit-lamp and IVCM (400 × 400 μm) findings after 6 months. A, Localized, less dense scar; (B) improved aspect of subbasal corneal nerve fibers, (C) reduced number of stromal needle-shaped structures, and (D) deep stroma close to endothelial layer—no fungal hyphae and *Acanthamoeba* cysts are detectable. (The full color version of this figure is available at www.corneajrnl.com.)

identification of microbial agents responsible for corneal infections is of utmost importance.

In fact, despite the culture of corneal samples remains a gold standard for the diagnosis of microbial keratitis,[4] it can require a long time to provide the results, especially for mycotic infections, and in some severe cases, the lack of a prompt, precise diagnosis may lead to severe consequences with visual loss.

Under this aspect, IVCM proved to be essential to provide a fast recognition of both *Acanthamoeba* and fungal infections to start an early, specific treatment.[5]

Acanthamoeba keratitis management is widely approved, and it can vary from PHMB and chlorhexidine to the diamide propamidine, the aminoglycoside neomycin and the antifungal clotrimazole.[6]

Recently the treatment with 0.66% povidone iodine was used in patients with corneal ulcer, demonstrating its efficacy as antimicrobial agent.[7] Conversely, poor information is available for the treatment of *P. curvatum* corneal infection. An in vitro study evidenced that low concentrations of voriconazole inhibit *Phialemonium* species.[6] In our patient, topical 1% voriconazole together with PHMB proved effective in the treatment of the combined *P. curvatum* and *Acanthamoeba* keratitis. Interestingly, in a recent report, voriconazole was proposed as an additional therapy for *Acanthamoeba* keratitis.

In fact, voriconazole demonstrated to be an effective inhibitor of 14-alfa-demetylase, a crucial enzyme for the synthesis of ergosterol, which is typically present in the *Acanthamoeba* membrane. Thanks to these properties because it blocks throphozoites proliferation, inhibits the progression to cysts formation, and also proved to have a cysticidal effects.[8] A successful treatment of resistant *Acanthamoeba* keratitis with 1% voriconazole was reported, and its use as an adjuvant therapy was suggested.[9]

Recently, a good clinical outcome with adjuvant topical 1% voriconazole combined with the first-line therapy in patients with *Acanthamoeba* keratitis was reported.[8]

To date, only 3 cases of ocular *P. curvatum* infection were described in the literature—all of them with devastating clinical results.[1–3] Two of them presented with endophthalmitis resulted from the use of contaminated therapeutic agents administrated for erectile dysfunction. In these patients, the infection was treated with intravitreal injections of amphotericin B. The third case presented corneal infection consequent to cataract surgery with a phacoemulsification procedure. Topical therapy with amphotericin B and natamycin was administered in association to the oral therapy with ketoconazole proved ineffective and required keratoplasty. The recurrence of infection occurred and was treated with intravitreal and intracameral amphotericin B without recovery. In these few reported cases, no voriconazole was used as in our therapeutic proceeding that followed the most recent literature recommendations.

To our knowledge, this is the first report of corneal infection caused by coexisting *P. curvatum* and *Acanthamoeba*. It is important to highlight that in our patient, a good clinical outcome was achieved; thanks to a prompt treatment administered in the early phase of the infection with a relatively small corneal infiltrate.

Complete corneal healing and visual recovery demonstrated how an early diagnosis with IVCM and the immediate, intensive, specific, and long-term treatment are crucial for the preservation of visual function in such a rare, combined microbial infection.

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