monitoring and referred quickly if vision decreases after BT injection, as it can lead to visual complications. Endothelial cell count should be monitored, and amantadine stopped if endothelial cell change occurs to avoid irreversible damage. In the rare event of a rapid and irreversible corneal decompensation occurring in a patient with previous LASIK, prompt endothelial graft should be considered before epithelial ingrowth further complicates restoration of vision.

Philippe Gros-Louis,* Stéphane Charest,† Marie Eve Légaré*,‡

*Laval University, Quebec City, Que.; †Centre Intégré Universitaire de Santé et Service Sociaux de la Mauricie et du Centre du Québec, Trois-Rivières, Que.; ‡CHU de Québec, Quebec City, Que.

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Correspondence to:
Marie Eve Légaré, MD FRCSC marie-eve.legare@fmed.ulaval.ca.

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Footnotes and Disclosure

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Intrastromal voriconazole for refractory infectious crystalline keratopathy associated with *Candida pararugosa*

Infectious crystalline keratopathy (ICK) is an infrequent complication of long-term topical steroid use following penetrating keratoplasty,[1] classically caused by *Streptococcus viridans*.[2] It has been reported in association with local immunosuppression after any ocular surgery (lamellar keratoplasty, cataract surgery, trabeculectomy, corneal cross-liking, and laser in situ keratomileusis), as well as in contact lens wearers, herpetic and *Acanthamoeba* keratitis, and corneal anaesthesia.[3,4] Besides α-haemolytic streptococci,[2] multiple additional microorganisms have been causally linked to ICK, including Gram-positive or -negative bacteria, atypical mycobacteria, and fungi,[3] most of them bearing biofilm-forming capacity. We hereby report an association between ICK and a rare *Candida* species, highlight some of the major challenges in diagnosis and treatment of ICK, and demonstrate effectiveness of intrastromal antifungal treatment for refractory keratitis.

A 60-year-old man complained of left ocular pain. He had presented 10 months previously with impending corneal perforation owing to descemetocele secondary to recurrent herpes simplex virus (HSV) keratitis. At that time, following consideration of treatment options,[5] the patient underwent left phacoemulsification and intraocular lens implantation combined with penetrating keratoplasty. He had no additional ophthalmic or medical history. He was on topical preserved dexamethasone 4 times daily OS and oral aciclovir 400 mg twice daily *per os*. At presentation, best-corrected visual acuities (BCVAs) were 20/30 OD and 20/40 OS. The right eye was normal. Examination of the left eye showed a stellate branching opacity within the paracentral donor corneal stroma (Fig.1A, 1B) with no overlying epithelial defect. There was marked left anterior chamber inflammatory activity (3+ cells) with no hypopyon. Clinical findings were suggestive of ICK. A suture associated with the lesion was removed, dexamethasone discontinued, and intensive topical ciprofloxacin and teicoplanin treatment initiated. Of note, left intraocular pressure (IOP) was 45 mm Hg, requiring treatment with a short course of oral acetazolamide and topical dorzolamide and timolol. Nine days later, IOP decreased to 5 mm Hg and subsequently normalized without requiring further treatment for the duration of follow-up period.

Serial corneal impression membrane sampling failed to uncover a causative microorganism, and the patient was empirically treated for several months with various combinations of antimicrobial, antifungal, and antiviral agents, which included oral aciclovir and doxycyline, and topical aciclovir, chloramphenicol, ciprofloxacin, teicoplanin, and voriconazole. The patient remained comfortable during this period and reported satisfactory compliance to prescribed treatment. Clinical findings remained stable with above treatments until 19 weeks later when there was evidence of progression (Supplementary Fig. 1A, available online). This prompted a corneal biopsy and intrastromal injection of vancomycin and cefuroxime. Culture and genomic analysis (the latter for 16S and 18S ribosomal RNA, and HSV) of

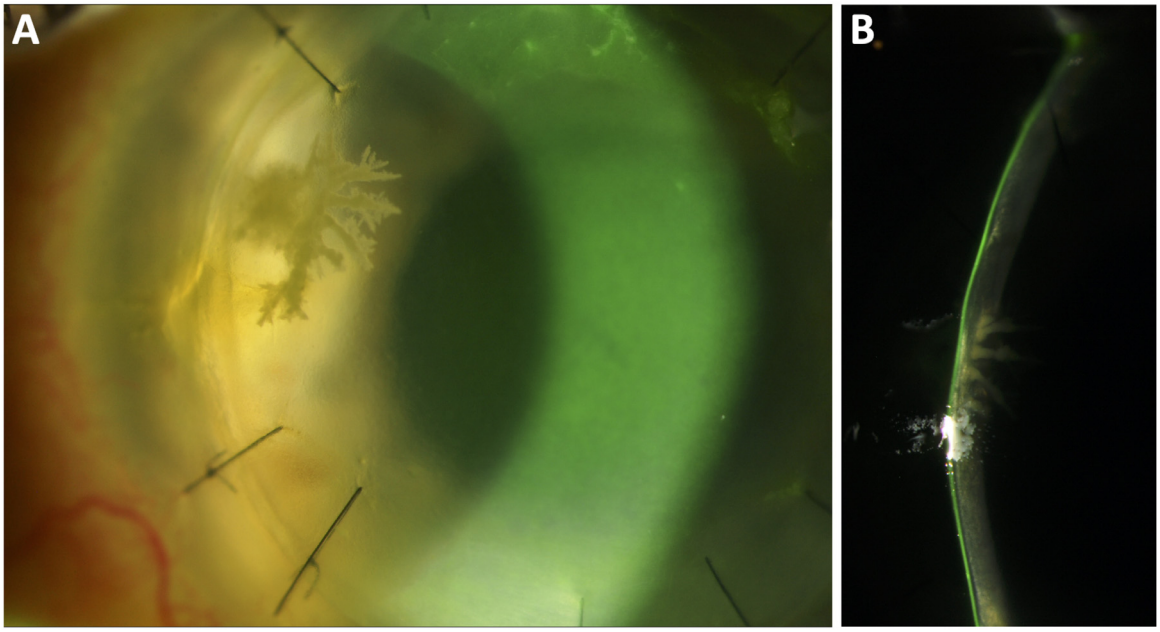

Fig. 1—Initial presentation of infectious crystalline keratopathy complicating penetrating keratoplasty. (A) "Snowflake"-like opacity with branching processes is evident within the paracentral corneal graft. (B) Slit examination demonstrates the midstromal localization of the opacity. Note the absence of significant inflammatory stromal reaction.

biopsy material did not isolate or identify microorganisms (bacteria, fungi, protozoa, or viruses), therefore empirical treatment continued with oral aciclovir and topical voriconazole and moxifloxacin. Three weeks later, there was further progression of the stromal infiltrate (Supplementary Fig. 1B, available online). All treatments were stopped for 48 hours before taking a new corneal impression sample, which revealed the presence of 3 pathogens following prolonged culture: *Staphylococcus warneri*, *Staphylococcus epidermidis*, and *Candida pararugosa*. On sensitivity testing, both *Staphylococcus* species were susceptible to ciprofloxacin, gentamicin, and teicoplanin, while only *S. warneri* was sensitive to chloramphenicol. Additionally, *C. pararugosa* was found to be sensitive to voriconazole and amphotericin B. These results guided further management that included intrastromal voriconazole injection (administered twice within 5 days at 1% w/v) and topical treatment with voriconazole and ciprofloxacin. Seven days after the second intrastromal voriconazole injection, there was partial regression of stromal infiltration (Supplementary Fig. 1C). Five weeks later, topical dexamethasone treatment was reinstated in order to minimize the risk of graft rejection while continuing the prophylactic dose of oral aciclovir and topical voriconazole and ciprofloxacin. Supplementary Fig. 1D, available online, shows the left eye 5 weeks after topical steroid treatment was resumed. Three weeks later, the patient reattended because of left ocular pain and blurred vision, and examination revealed a large geographic ulcer (Supplementary Fig.1E, available online). HSV type 1 was identified by polymerase chain reaction on swab material sampled from the ulcer base, and despite treatment with oral aciclovir and topical ganciclovir, teicoplanin, ciprofloxacin, and voriconazole, he required emergency tectonic keratoplasty because of corneal perforation 13 days later. A variety of stains failed to reveal any bacteria or fungi on histological analysis of the removed corneal button. Supplementary Fig. 1F shows the left eye 6 days following surgery. At final follow-up (12 weeks after tectonic keratoplasty and 54 weeks following initial presentation), the patient remained stable on treatment with oral aciclovir and topical dexamethasone only, and his left BCVA was 20/80.

Despite a well-established pathogenic association of ICK with a wide variety of microorganisms, low diagnostic yield of microbiological sampling is frequently encountered.[3,6] This was particularly obvious in our patient in which serial microbiological samples tested negative. It is possible that the absence of an epithelial defect and the deep stromal localization of the crystalline pathology may account for the poor yield of impression membrane sampling. Nevertheless, in our experience corneal impression sampling is associated with a higher rate of microorganism isolation compared with corneal scraping.[7] Importantly, even a corneal tissue biopsy tested negative. This lack of microbiological guidance hampered our therapeutic efforts until the identification of *Candida pararugosa* in a corneal impression sample dictated further treatment with intrastromal voriconazole as guided by sensitivity testing. Because of the simultaneous isolation of *Staphylococcus epidermidis* and *Staphylococcus warneri*, we persisted with topical antibiotic therapy. Although all 3 identified pathogens can form biofilms, it remains obscure whether all contributed to the clinical findings, or the emergence of both skin commensal *Staphylococcus* species after long culture represented sample contamination. Nevertheless, the lack of response to initial

intrastromal antibiotic delivery and the temporary clinical improvement induced by intrastromal voriconazole both suggested a role for the rare *Candida* species in our case. Such effectiveness of intrastromal voriconazole has been previously demonstrated in fungal keratitis nonresponsive to topical treatment;[8] however, such approach is rarely employed in practice. The transient response in our case was compromised by the development of a herpetic geographic ulcer (presumably precipitated by reinstatement of topical steroids) while on prophylactic aciclovir use, and it would be tempting to consider the possibility of a resistant HSV strain as previously described.[9] Despite this unfortunate outcome, we would like to propose that intrastromal treatment corroborated by sufficient microbiological evidence can be a safe and effective therapeutic approach to any refractory keratitis.

Different *Candida* species have been previously linked to ICK. Wilhelmus and Robinson presented 2 cases in corneal transplant recipients, each associated with combined infection by both *Candida albicans* and a *Staphylococcus* species.[10] Both patients responded well to withdrawal of topical steroids and intensive treatment with topical amphotericin B and topical antibiotics as well as oral ketoconazole, obviating the need for repeat keratoplasty.[10] Rhem and colleagues reported a case of ICK caused by *Candida parapsilosis* in a penetrating keratoplasty, which was treated for several months with topical amphotericin B and oral ketoconazole and eventually required repeat corneal transplantation.[11] Interestingly, long antifungal treatment for over 6 months was insufficient to eradicate the underlying infection, as indicated by the detection of fungi within the removed corneal button.[11] Touzeau and colleagues presented a patient who developed recurrent ICK in 2 consecutive corneal grafts of the same eye.[12] Notably, *Streptococcus viridans* was isolated during the first episode, followed by identification of *Candida albicans* in the repeat penetrating keratoplasty.[12] Despite treatment with topical amphotericin B and oral fluconazole, ICK gradually progressed to corneal scarring and vascularization.[12]

Susceptibility testing suggested that the isolated *Candida pararugosa* in our patient was sensitive to both voriconazole and amphotericin B. Interestingly, sensitivity analysis of different *Candida* species isolated from corneal scrape samples, suggested superiority of amphotericin B,[13] consistent with previous case reports demonstrating its beneficial intrastromal application.[14,15] Determining susceptibility or resistance relies on identifying the lowest drug concentration required to suppress growth of a specific isolate in the laboratory and comparing this minimum inhibitory concentration (MIC) with the "breakpoint" MIC separating sensitive and resistant strains.[16] It is essential to note that breakpoint MIC corresponds to drug concentration in serum following systemic administration;[16] therefore, caution is needed when correlating with anticipated therapeutic outcomes of drop instillation or intrastromal injection in the context of infectious keratitis.[17] Finally, *Candida pararugosa* is a rare species and assessing its susceptibility to antifungal agents depends on comparisons with clinical breakpoints established for *Candida albicans*,[18] further emphasizing the need for cautious interpretation of sensitivity testing.

In summary, we have presented a case of ICK associated with *Candida pararugosa*. To our knowledge, this pathogen has not been previously reported to cause keratitis. Despite this novel association, poor efficiency of microbiological sampling and inadequate response to topical antibiotic and antifungal agents in our report, both recapitulate recurring themes in managing most cases of ICK. Although clinical diagnosis is usually straightforward on the basis of observing the typical stromal branching opacities, variable clinical presentations of ICK with or without an epithelial defect have been reported in the literature.[1,2,6] Breach of the epithelial barrier (such as that occurring during corneal suturing) is necessary for access of causative microorganisms into the corneal stroma, nevertheless the presence or absence of an epithelial defect cannot reliably predict the identity of the underlying causative infectious agent(s). As their isolation can be burdensome, appropriate treatment can also be extremely challenging. Steroid withdrawal and topical broad-spectrum antibiotics are reasonable initial steps; however, in cases occurring within corneal grafts, it is essential to first differentiate between ICK and transplant rejection. Refractory cases may subsequently require intrastromal antimicrobial or antifungal agents, keratectomy, or repeat keratoplasty.[1–3]

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2021.02.023.

Eleftherios I. Agorogiannis,*,† Stephen B. Kaye,* Esmaeil Arbabi*

*St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom; †Moorfields Eye Hospital, London, United Kingdom.

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Correspondence to:
Eleftherios I. Agorogiannis, DPhil, FRCOphth: eleftherios.agorogiannis@gmail.com.

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Footnotes and Disclosure

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