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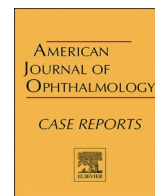
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Povidone iodine-infused pars plana vitrectomy for severe *Arthrographis kalrae* fungal endophthalmitis

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ABSTRACT

Purpose: *Arthrographis kalrae* is an opportunistic fungus that can cause a severe and atypical endophthalmitis. In limited studies, low-dose povidone iodine has been shown to be effective in treating fulminant bacterial endophthalmitis. In this case report, we describe the successful treatment of recalcitrant *Arthrographis kalrae* keratitis-associated endophthalmitis with intraocular povidone iodine during pars plana vitrectomy.

Observations: A patient with *Arthrographis kalrae* keratitis-associated endophthalmitis had persistent disease despite aggressive medical management. The infection resolved following pars plana vitrectomy with infusion of dilute povidone iodine. No toxicity was noted postoperatively.

Conclusions and importance: Povidone iodine-infused pars plana vitrectomy offers promise as a treatment for infectious endophthalmitis that fails medical management. This is the first report demonstrating eradication of fungal endophthalmitis using povidone iodine-infused pars plana vitrectomy.

1. Introduction

Exogenous fungal endophthalmitis is an uncommon and vision-threatening intraocular infection that is commonly associated with fungal keratitis.¹ Filamentous molds, namely *Fusarium* and *Aspergillus*, account for the majority of culture-positive keratitis-associated endophthalmitis.² Visual outcomes are variable. The addition of low-dose povidone iodine to balanced salt solution during pars plana vitrectomy has been shown to be nontoxic to the retina and effective in treating severe bacterial endophthalmitis.^{3,4} Here, we present a unique case of recalcitrant *Arthrographis kalrae* keratitis-associated endophthalmitis successfully treated with povidone iodine-infused pars plana vitrectomy.

2. Case report

A 61-year-old Caucasian man was referred for evaluation of a large central corneal ulcer in his left eye. Ocular history was significant for proliferative diabetic retinopathy, previously treated with panretinal photocoagulation, and diabetic macular edema, for which he was receiving both intravitreal anti-VEGF and intravitreal dexamethasone implant (Ozurdex) injections in the left eye. He was also a soft contact lens user, with a reported history of poor contact lens hygiene.

On presentation, his visual acuity was hand motion in the left eye and intraocular pressure was 14 mm Hg. A large central non-suppurative stromal infiltrate with an overlying epithelial defect was observed on slit lamp biomicroscopy (Fig. 1A). There was a poor view to the fundus due to corneal opacification. Examination of the right eye was unremarkable. Corneal scrapings were obtained and an intensive regimen of hourly topical fortified ceftazidime 50 mg/ml and tobramycin 40 mg/ml was initiated pending culture results. Subsequently, his cultures returned positive for *Arthrographis kalrae* and his antimicrobial treatment was switched to topical natamycin 5 % administered every 2 h. The fungal isolate was found to be susceptible to natamycin, amphotericin B and voriconazole and his current antifungal regimen was continued. Initially, there was consolidation of his central stromal infiltrate with some improvement in his pain (Fig. 1B). However, seven weeks into treatment, there was clinical regression with a worsening infiltrate and a new hypopyon despite maintaining an every 2 h topical antifungal regimen (Fig. 1C). Repeat corneal scrapings were obtained, which were persistently positive for *A. kalrae* and a trial of intra-stromal amphotericin B (5 mcg) was given. Unfortunately, the hypopyon persisted which was concerning for posterior extension of his infection. B scan ultrasonography had demonstrated no vitreous involvement (Fig. 2A), but given the deteriorating anterior segment exam, a vitreous tap and intravitreal injection of voriconazole were performed. Shortly

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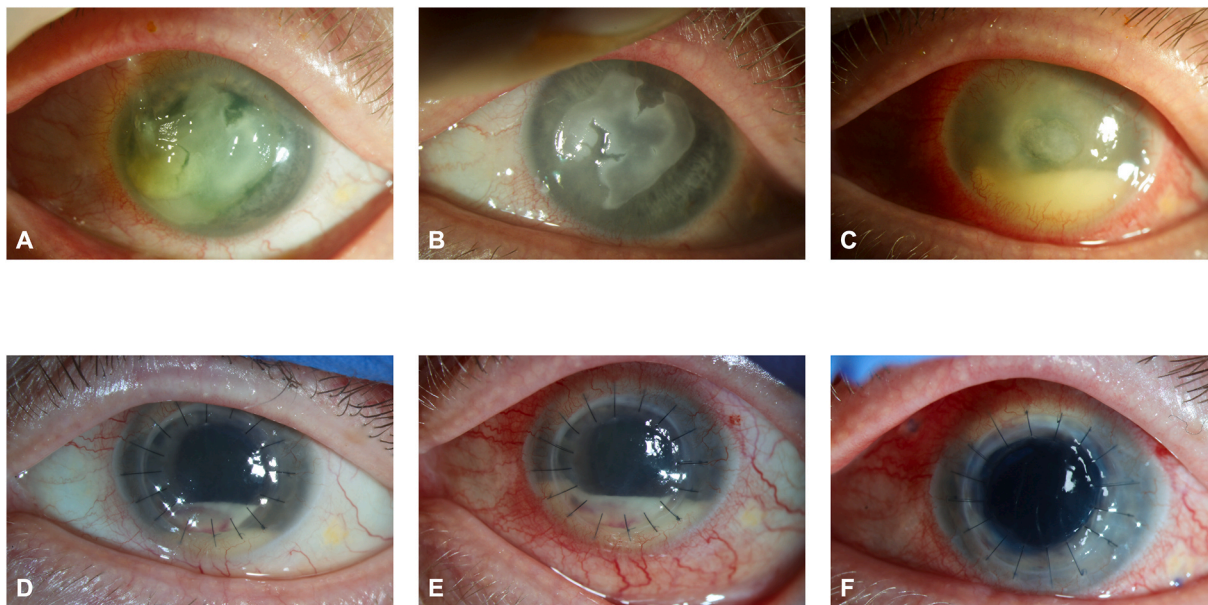


Fig. 1. Slit lamp photographs demonstrate a severe fungal keratitis progressing to endophthalmitis despite maximal medical therapy requiring surgical intervention. (A) Initially, the patient presented with a large central stromal infiltrate. (B) Over the first few weeks, there was consolidation of the infiltrate with aggressive topical antifungal therapy. (C) However, the patient developed a new hypopyon and worsening pain seven weeks into treatment. (D) The hypopyon persisted despite a therapeutic penetrating keratoplasty but was controlled with serial intravitreal amphotericin B injections. (E) There was enlargement of the hypopyon and increased conjunctival injection with an attempt to increase the frequency of injections from three to five days. (F) Ultimately, a repeat penetrating keratoplasty with povidone iodine-infused pars plana vitrectomy cleared the infection.

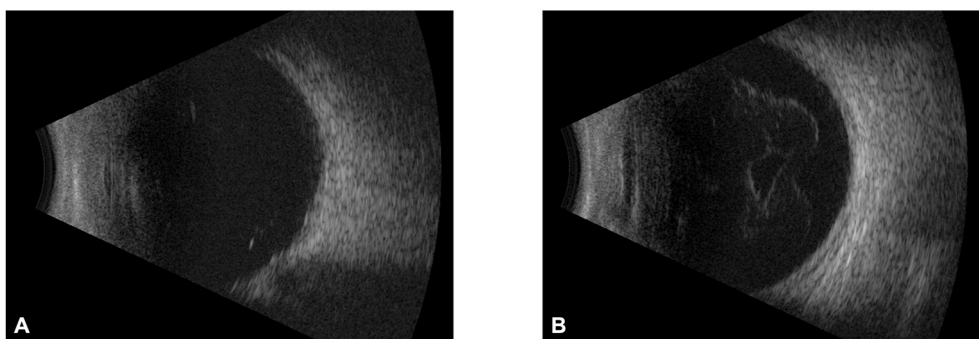


Fig. 2. (A) B scan ultrasonography performed when the patient developed a new hypopyon revealed no vitreous debris. (B) Following his first therapeutic penetrating keratoplasty, serial B scans demonstrates worsening vitreous debris concerning for endophthalmitis.

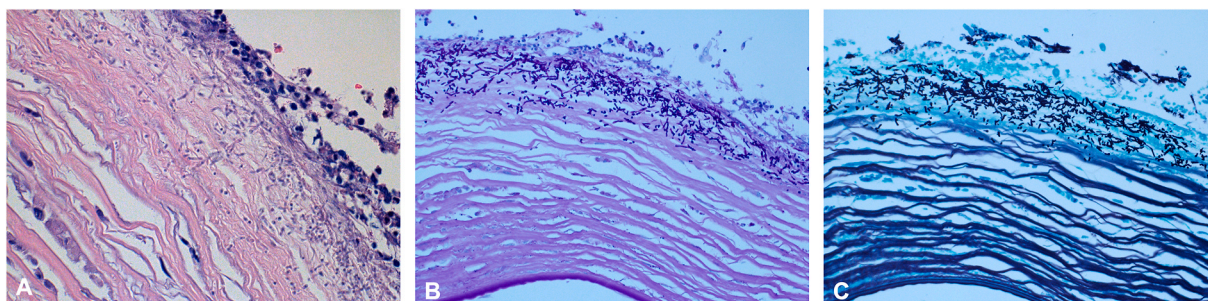


Fig. 3. Histopathologic examination of the patient's cornea reveals (A) septate fungi with an acute branching pattern infiltrating into deep stromal tissue, staining positively with (B) period-acid Schiff and (C) Grocott's methenamine silver.

after, a therapeutic penetrating keratoplasty was performed for primary control of fungal keratitis. Surgical pathology revealed septate hyphae diffusely infiltrating the deep corneal stroma, consistent with fungal keratitis (Fig. 3).

Despite the surgery, the hypopyon persisted and the patient

continued to have significant pain (Fig. 1D). A repeat aqueous tap was negative and intravitreal injections of ceftazidime, vancomycin and voriconazole were subsequently performed. Over the next month, the patient received a total of ten intravitreal amphotericin B injections as well as treatment with oral voriconazole 200 mg daily. Despite initial

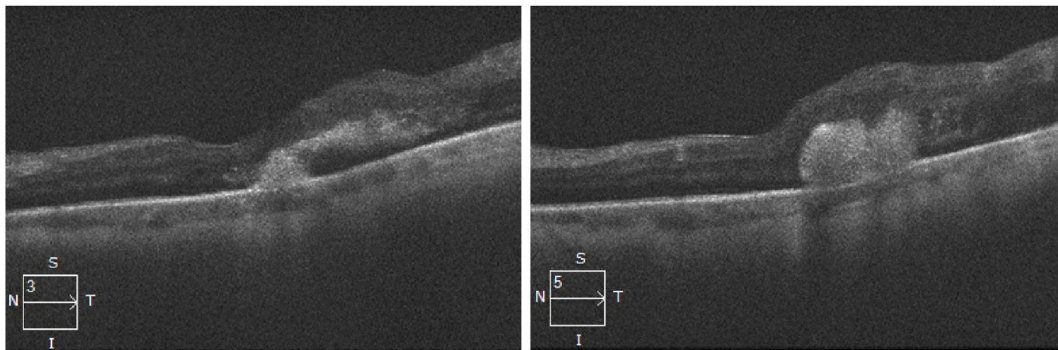


Fig. 4. Following pars plana vitrectomy for endophthalmitis, a large area of subretinal macular fibrosis was revealed. Optical coherence tomography shows subretinal hyper-reflective material (SHRM) corresponding to the fovea-involving macular scar.

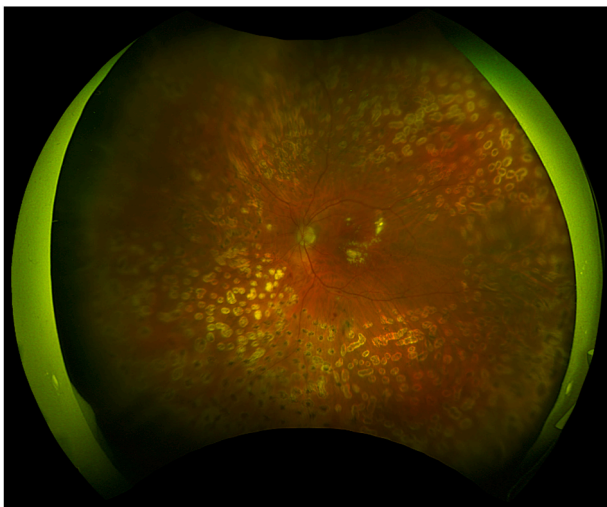


Fig. 5. There has been no disease recurrence one year after povidone iodine-infused pars plana vitrectomy. Ultra-widefield fundus imaging shows no vitreous debris, a stable macular scar and well-treated panretinal photocoagulation for proliferative diabetic retinopathy.

improvement on this regimen, the patient subsequently developed worsening conjunctival injection, vitreous debris and enlargement of the hypopyon when the interval of intravitreal amphotericin B injections was extended from three to five days (Fig. 1D and E). This suggested that the infection was controlled on an intensive every three-day injection interval, and worsened with an attempted extension to every five days. Given this treatment regimen was not practically feasible long-term, we elected to proceed with surgical intervention. In addition, he had now developed a significant cataract that further limited the view to the posterior segment. A repeat therapeutic penetrating keratoplasty, lensectomy, and pars plana vitrectomy were performed. A temporary keratoprosthesis was used for visualization. During the vitrectomy, 1.25 mL (0.025 %) of 10 % povidone iodine was added to a 500 mL bottle of balanced salt solution (Alcon Laboratories, Forth Worth, TX) 15 minutes prior to incision. The eye was continuously and only irrigated with PI-infused BSS for the duration of the surgery.

Intraoperatively, the vitreous was noted to be turbid and a vitreous sample was sent for cultures, which ultimately demonstrated no bacterial or fungal growth. During lensectomy, the capsular bag was removed in its entirety in case of biofilm formation, though this was not clinically apparent. Following core vitrectomy, a subretinal macular scar was visualized. This macular scar of unclear chronicity, possibly due to the infection, ultimately limited his final visual acuity (Fig. 4). Scattered intraretinal hemorrhages and panretinal photocoagulation scars were also observed, consistent with his history of proliferative diabetic

retinopathy.

Following the repeat penetrating keratoplasty and povidone iodine-infused vitrectomy, the endophthalmitis resolved (Fig. 1F). Histologic examination of the failed graft did not show recurrent fungal elements. His clinical course stabilized with resolution of the hypopyon and rapid improvement in pain. His postoperative visual acuity improved to 20/400. One year following vitrectomy, there has been no recurrence of fungal keratitis or endophthalmitis. Posterior segment exam revealed a clear vitreous, normal appearing disc, a stable macular scar, and panretinal photocoagulation scars (Fig. 5).

3. Discussion

Arthrographis kalrae is a rare opportunistic pathogen of the eye. Including our patient, there are eight published reports of *A. kalrae* ocular infections and only one other documented case of endophthalmitis. Here, we highlight the recalcitrant clinical course of treating this unusual fungal infection and present a successful case of povidone iodine-infused irrigation during pars plana vitrectomy as adjuvant antimicrobial therapy for severe keratitis-associated endophthalmitis.

There are shared risk factors among the published cases of *A. kalrae* ocular infection including contact lens use, trauma or exposure to soil contaminants.⁵⁻⁹ Contact lens use is a well-documented non-traumatic risk factor of fungal keratitis, and has recently been more commonly associated with the *Fusarium* species.¹⁰⁻¹² In the presented case, the patient reported both long term soft contact lens use and poor contact lens hygiene. Underlying immunosuppression is also implicated in fungal infections including *A. kalrae*, as seen in a case where the patient had a history of treated diffuse large B-cell lymphoma.¹³ Our patient was locally immunosuppressed with a history of intravitreal steroid injections for diabetic macular edema prior to presentation, which not only predisposed him to an opportunistic infection but may have also compromised his recovery.

The functional and anatomic outcomes following *A. kalrae* infection are guarded. In the existing literature, 2 (25 %) of the 8 eyes were ultimately enucleated and only one eye achieved a final visual acuity of 20/40 (Snellen) or better. Difficulty in identifying the pathogen, lack of consensus in treatment and a relentlessly progressive clinical course were common themes in the reported cases. In our case, despite aggressive multimodal therapy with three antifungal agents and sensitivity to these agents per microbial testing, he ultimately required two therapeutic penetrating keratoplasties and a pars plana vitrectomy to eradicate the infection. Therapeutic keratoplasty has previously been shown to have up to 90 % success rate in treating refractory fungal keratitis.¹⁴ Interestingly, no fungi were seen on histologic examination of the failed graft in our patient, indicating that the first surgery was successful in eliminating the fungal keratitis. Resolution of the infection following pars plana vitrectomy suggests that his persistent hypopyon and vitreous debris were likely secondary to an infectious

endophthalmitis. It is not surprising that his vitreous biopsy was negative, given the difficulty in isolating *Arthrographis* species and prior intravitreal antifungal treatment. Furthermore, removal of the capsular bag during vitrectomy may have an important role in disease eradication. In literature, histopathology of enucleated specimens has shown that fungal hyphae can traverse the lens capsule, serving as an insidious nidus for persistent infection.¹³

Currently, there is no standard of care for severe and atypical infectious endophthalmitis. Frequently, these patients require multiple vitreoretinal procedures due to recalcitrant inflammation or infection and have poor final visual outcomes.¹⁵ Intraocular povidone iodine has recently been suggested as a possible adjuvant antimicrobial agent to a limited armamentarium for treating these difficult cases.¹⁶ Outside of the eye, povidone iodine is ubiquitous as the first line antiseptic medication for sterilizing the ocular surface prior to intraocular procedures. In vivo rabbit models have shown that the maximum nontoxic concentration of intraocular povidone iodine is 0.027 %, with no functional retinal toxicity by electroretinography or anatomical damage by histological analysis.¹⁷ This is well above the 0.005 % threshold needed for a 100 % bactericidal effect; while comparatively less is known about its fungicidal properties, 0.005 % povidone iodine retains robust antifungal activity against *Candida* species with up to a 99.4 % reduction in microbial load.¹⁸ It is plausible, then, that 0.025 % povidone iodine can achieve complete sterilization of a fungal infection as seen in our case without inadvertent retinal toxicity. We note, however, that patient's subretinal macular scar limits our ability to evaluate for potential foveal damage from intraocular betadine.

The use of multiple antifungals is prudent in the treatment of a virulent pathogen such as *Arthrographis kalrae* and we suggest that povidone iodine may be an effective addition to conventional treatment options. In addition to its broad antimicrobial properties, there are no known mechanisms of resistance to povidone iodine likely due to its numerous and simultaneous molecular targets.¹⁹ This may emphasize its role in the treatment of recalcitrant infections in which conventional treatments are ineffective.

4. Conclusions

Povidone iodine-infused pars plana vitrectomy is an innovative treatment for recalcitrant infectious endophthalmitis. Vitreoretinal surgeons may consider its use in such cases.

CRedit authorship contribution statement

Denis Huang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Lillian Tran:** Data curation. **Jennifer YH. Li:** Data curation. **William Lee:** Data curation. **Esther Kim:** Formal analysis, Data curation. **Kareem Moussa:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Disclosures

None.

Conflicts of interest

The following authors have no financial disclosures: DH, LT, JL, WL, EK, KM.

Authorship

"All authors attest that they meet the current ICMJE criteria for Authorship."

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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