Case Report

Endophthalmitis Caused by *Agrobacterium radiobacter* following Intravitreal Aflibercept for Diabetic Retinopathy

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Keywords

Agrobacterium radiobacter · Endophthalmitis · Aflibercept

Abstract

Agrobacterium (Rhizobium) radiobacter is a gram-negative bacillus rarely implicated in ocular disease. A 79-year-old male who performed extensive yardwork following intravitreal injection with aflibercept for diabetic macular edema developed endophthalmitis caused by *Agrobacterium radiobacter* on post-injection day 7. The patient was treated with vitreous tap and intravitreal injection of vancomycin and ceftazidime with clearance of the infection and restoration of his baseline visual acuity at 20/80.

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Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is the mainstay of treatment for many retinal diseases [1]. Although rare, endophthalmitis is a feared complication of anti-VEGF treatment, with an incidence ranging from 0.013% to 0.061% [2–4]. The most frequently identified pathogens causing endophthalmitis after intravitreal anti-VEGF treatment are coagulase-negative staphylococci, *Streptococcus viridans*, and *Staphylococcus*

aureus [2, 5], with significant vision loss often associated with streptococcus infection [2]. The most significant risk factor for endophthalmitis is violation of aseptic technique during injection [6–9]. Other potential risk factors include anterior chamber paracentesis and eyelid manipulation prior to injection [10, 11].

Agrobacterium (Rhizobium) radiobacter is an aerobic gram-negative bacillus predominantly found in soil [12]. Systemic infection due to *Agrobacterium radiobacter* is rare and most commonly occurs in immunocompromised patients [13–17]. While *Agrobacterium radiobacter* endophthalmitis has been reported, most cases have occurred after cataract surgery [18–22]. *Agrobacterium radiobacter* endophthalmitis after aflibercept injection following a potential post-treatment soil exposure is described.

Case Report/Case Presentation

A 79-year-old male with past medical history of insulin-dependent type II diabetes mellitus and past ocular history of moderate nonproliferative diabetic retinopathy with clinically significant macular edema presented to the retina clinic complaining of decreased vision and pain in the right eye. The patient was undergoing regular treatment with intravitreal aflibercept and received his most recent injection 7 days prior to presentation. All injections were performed in the office after povidone iodine prep. He was not immunosuppressed but admitted to trimming extensive foliage throughout his property the same day after receiving his most recent injection.

On exam, visual acuity was hand motion in the right eye, decreased from a baseline of 20/80. He was noted to have corneal stromal haze, mutton-fat keratic precipitates, 3+ anterior chamber cell, and a 0.5-mm hypopyon with fibrin in the pupillary margin. Posterior chamber intraocular lens was in place. Funduscopy exam revealed vitreous debris and posterior cells. B-scan demonstrated hyperechogenicity of the vitreous and vitreous echoes without signs of retinal detachment (Fig. 1). Optical coherence tomography (OCT) demonstrated diminished signal transmission (Fig. 2a, b).

Vitreous samples were collected via needle aspiration and intravitreal vancomycin and ceftazidime were administered. The vitreous culture demonstrated *Agrobacterium (Rhizobium) radiobacter* and the patient was started on oral azithromycin and levofloxacin. At the 1-month follow-up, visual acuity had returned to baseline of 20/80 and the infection had resolved (Fig. 2c).

Discussion/Conclusion

Agrobacteria are gram-negative bacilli known to cause tumors in plants [19]. The first case of human infection with *Agrobacterium radiobacter* was described in 1980 in a patient with endocarditis [23] and the first case of endophthalmitis due to *Agrobacterium radiobacter* was reported in 1996 following cataract surgery [19], with few reports since then [18, 20–22, 24].

Predominantly found in soil, the development of *Agrobacterium radiobacter* endophthalmitis has been associated with outdoor activities after cataract surgery [19, 21]. To our knowledge, exposure to soil following intravitreal injection has not been described as a purported cause of endophthalmitis. This is a possibility in our case given the patient's performance of yardwork following injection and the known association between soil exposure and

Agrobacterium radiobacter endophthalmitis after cataract surgery [19, 21]. Indeed, patients who have undergone either intraocular surgery or intravitreal injection should be encouraged to avoid outdoor activity involving potential exposure to soil immediately following the procedure [21].

While most systemic infections due to *Agrobacterium radiobacter* tend to occur in immunocompromised patients [13–17], all reported cases of *Agrobacterium radiobacter* endophthalmitis have occurred in the absence of immune suppression [18–22, 24]. This tendency to cause endophthalmitis in the absence of immunosuppression, particularly after intraocular lens implantation, has been attributed to *Agrobacterium radiobacter*'s propensity to adhere to silicone substances such as intraocular lens implants [21, 25]. Small quantities of silicone oil droplets are indeed present in intravitreal anti-VEGF injections [26]. However, their presence is unlikely to predispose to infection, as silicone oil has demonstrated antimicrobial activity and may in fact be beneficial in cases of endophthalmitis associated with retinal detachment requiring vitrectomy [27, 28].

The clinical presentation of *Agrobacterium radiobacter* endophthalmitis is similar to endophthalmitis caused by other microorganisms, with common findings including decreased vision, pain, hypopyon, and vitreous opacities. Diagnosis is ultimately confirmed by isolation of the pathogen via vitreous or aqueous humor sampling. While isolation of *Agrobacterium radiobacter* is possible after 2 to 3 days of incubation on blood-enriched media or MacConkey agar, difficulties in phenotypic identification may delay results or even cause incorrect identification [20, 21]. As such, a faster and more accurate method involving RNA sequencing may be utilized in cases requiring rapid diagnosis, although culture remains necessary for susceptibility testing [20, 29].

While *Agrobacterium radiobacter* is an organism of low virulence [19, 22], it possesses a variety of mechanisms for antimicrobial resistance, possibly as a result of its coexistence with antibiotic-producing organisms in soil [21, 30, 31]. Susceptibility patterns include frequent resistance to tobramycin and occasional resistance to other common antimicrobial agents such as trimethoprim-sulfamethoxazole, ampicillin, gentamicin, amikacin, ceftazidime, and vancomycin [12, 15, 21]. This tendency for resistance against antimicrobial agents approved for intravitreal injection may underscore the importance of oral antibiotic therapy as an adjunct to intravitreal treatment of *Agrobacterium radiobacter* endophthalmitis [21]. Some have suggested an empiric antibiotic regimen of intravitreal aminoglycosides such as amikacin in conjunction with oral carbapenems and fluoroquinolones in the treatment of endophthalmitis after cataract surgery [20, 21]. Indeed, cases of *Agrobacterium radiobacter* endophthalmitis refractory to classic empiric antimicrobial therapy have been reported after cataract surgery, ultimately requiring pars plana vitrectomy and, in one case, removal of intraocular lens implant [20, 21]. As such, careful consideration of the most appropriate antibiotic regimens in conjunction with antimicrobial susceptibility patterns is essential in preserving visual potential in patients with *Agrobacterium radiobacter* endophthalmitis [18, 20, 22, 24]. As demonstrated previously in neovascular age-related macular degeneration, our patient's OCT findings prior to anti-VEGF injection improved after treatment of his endophthalmitis [32].

In summary, *Agrobacterium radiobacter* is a soil-dwelling organism that rarely causes disease in humans. Soil exposure has been associated with endophthalmitis following cataract surgery but not intravitreal injection. A patient with *Agrobacterium radiobacter* endophthalmitis following intravitreal aflibercept injection is described. As such, we introduce soil exposure as a potential source of endophthalmitis following intravitreal injection and present the first known case of *Agrobacterium radiobacter* endophthalmitis after aflibercept injection.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient. The manuscript conforms to the tenets of the Declaration of Helsinki and does not include any information which may reveal the patient's identity.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Landon J. Rohowetz: data analysis and interpretation, manuscript drafting, and literature search. Nicolas A. Yannuzzi and Nimesh A. Patel: manuscript drafting and revision. Sunil Gupta and Darlene Miller: patient assessment, data collection, and manuscript revisions. Harry W. Flynn Jr.: manuscript conception, design, revision, and final approval.

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Fig. 1. B-scan demonstrating diffuse opacities and hyperechogenicity of the vitreous cavity.

Fig. 2. **a** Optical coherence tomography (OCT) on the day of aflibercept injection, demonstrating trace intraretinal fluid. **b** OCT 5 days after diagnosis of endophthalmitis, revealing globally diminished signal transmission with mild intraretinal fluid. **c** OCT 7 days after diagnosis of endophthalmitis demonstrating decreased intraretinal fluid and several hyperreflective preretinal foci.