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Intravitreal linezolid in the management of vancomycin-resistant enterococcal endophthalmitis

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ABSTRACT

Purpose: Linezolid is a synthetic antibiotic, the first of the oxazolidinone class, used for the treatment of infections caused by multi-resistant bacteria including *Streptococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). We report on a case of endophthalmitis caused by vancomycin-resistant *Enterococcus feacium* treated with intravitreal linezolid. It has proved efficacious in animal models but its safety in humans is not fully known.

Observations: An 84-year-old man who had phacoemulsification surgery and anterior chamber intraocular lens due to posterior capsule rent. Visual acuity (VA) following surgery was 6/24 uncorrected. The following week he developed signs of endophthalmitis, characterized by corneal infiltration and keratic precipitates, with anterior chamber and vitreous haze. Cultures yielded no growth, while repeated treatments with intravitreal vancomycin, ceftazidime, and amphotericin B did not control the infection. Vitrectomy was performed twice during the patient's course, with intravitreal amikacin injection after the second vitrectomy, but poor control of the endophthalmitis persisted. After several weeks of limited response to treatments, the diagnosis was finally made using Giemsa stain of direct smear which showed characteristic morphology of *Enterococcus faecium*. Linezolid, one of the oxazo-lidinones, was initially given in oral form 600 mg BID for three weeks, but did not prove efficacious. Subsequently, intravitreal linezolid 200 mcg in 0.1ml was injected, which cleared the vitreous and cornea infection within a week. However, there was a residual exudative detachment of the retina in the posterior pole, leaving the patient with a final vision of hand movement.

Conclusion and importance: Vancomycin-resistant enterococcus is a rare cause of endophthalmitis. Intravitreal linezolid is an effective treatment, but the subsequent exudative retinal detachment may have been related to this novel therapy.

1. Introduction

The incidence of endophthalmitis after cataract and other intraocular surgeries varies from country to country and from hospital to hospital.[1,2] Over the years, protocols have been developed to manage this condition, which depend on a successful vitreous tap and positive culture and sensitivity to guide treatment.[3,4] Most of the common causative organisms are sensitive to broad-spectrum antibiotics[5]; combination vancomycin (for gram positive organisms) and ceftazidime or amikacin (for gram negative organisms) are often the first line drugs.[4] In many cases, this usually suffices. But in some cases, there is poor response to this combination. In a series of endophthalmitis cases by Gentile et al.,[5] 99.7% of gram-positive bacteria were susceptible to vancomycin.

We encountered a case in which a patient developed endophthalmitis after a complicated phaco-emulsification procedure (posterior capsule rent) in which an anterior chamber intraocular lens (ACIOL) was placed. The endophthalmitis did not respond to the standard intravitreal vancomycin, ceftazidime and amphotericin B. In addition, the cultures came back negative, and we had to resort to a direct smear and KOH test to make a diagnosis. The direct smear showed a gram positive diplococcoid forms with a pale bisection, identifying *Enterococcus faecium*. This report details our encounter with this patient, and management with intravitreal linezolid, a synthetic antibiotic in the oxazolidinone class used for the infections with multi-resistant bacteria.

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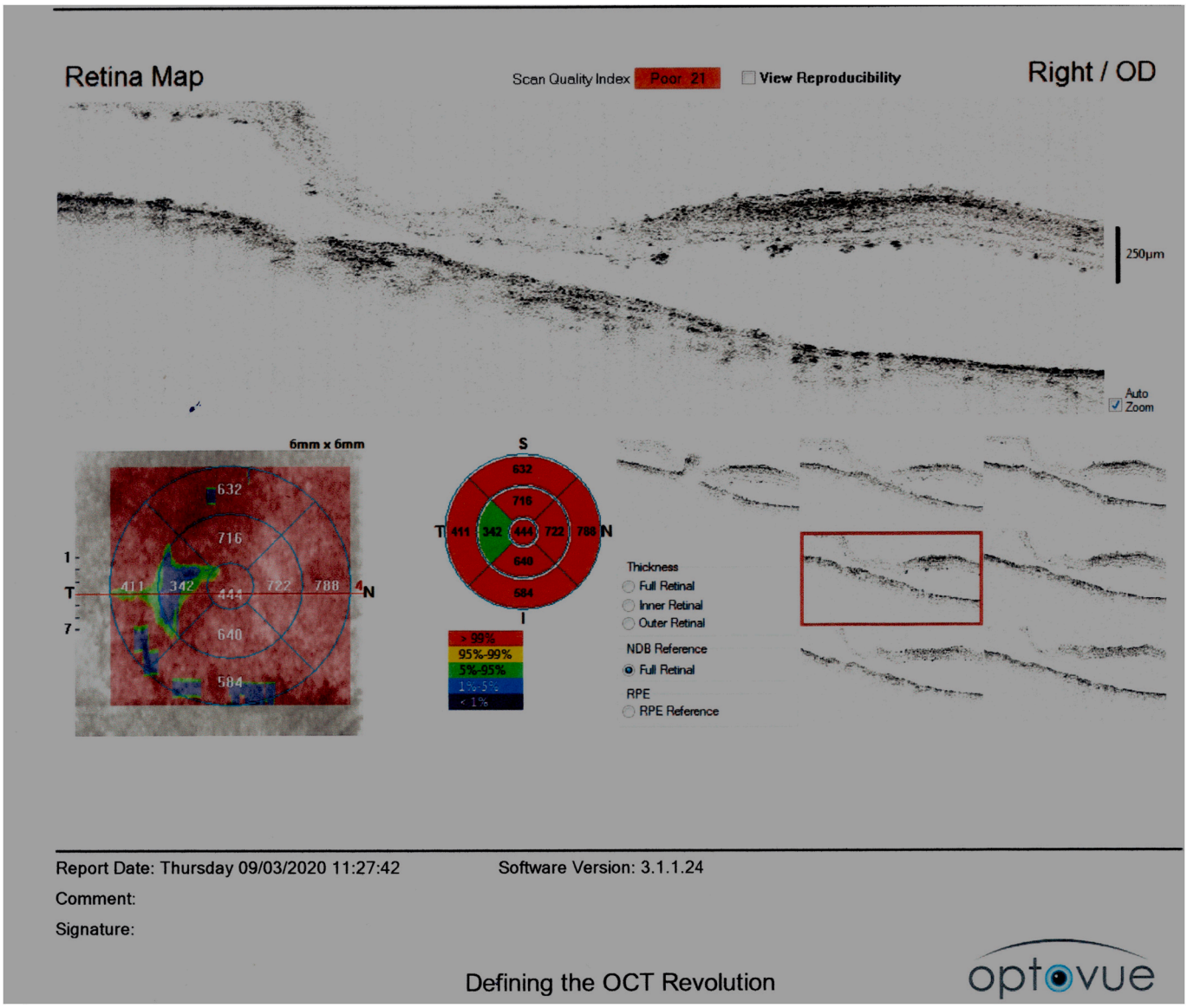

Fig. 1. Optical Coherence Tomogram of the Right eye of the patient showing localized detachment around the macula area (Inverse greyscale).

2. Case report

An 84-year-old man underwent phacoemulsification OD for moderate cataract using a clear corneal incision; the case was complicated by posterior capsule rent, and consequently, an ACIOL was placed. He was seen a week later with lacrimation and corneal edema and corneal infiltration with keratic precipitates, with anterior chamber and vitreous haze. There was no retinal reflex with indirect ophthalmoscopy. On the suspicion of endophthalmitis, a vitreous tap was obtained followed by intravitreal vancomycin 1mg and ceftazidime 2mg, both in 0.1 ml. The day after the injection, there was lid edema, conjunctival hyperemia, and corneal edema and striae, with worsened inflammatory reaction in the anterior chamber. Unfortunately, no growth was shown on vitreous cultures after 48 hours.

On the eleventh day post-operation, the corneal decompensation worsened. We repeated intravitreal vancomycin and ceftazidime, gave subconjunctival depomedrol (0.5ml containing 20 mg of methyl) and placed a bandage soft contact lens to manage the superficial corneal disease. On the fourteenth post-operative day, with no improvement, amphotericin B injection was given intravitreally on the suspicion that this might be a fungal endophthalmitis. Oral fluconazole 200mg BID was also introduced.[6] On post-operative day 16, still without significant improvement, the decision was made to perform three-port posterior vitrectomy, with repeat vancomycin injection, obtaining another sample for microscopy, culture and sensitivity. At the end of the procedure, a clear view of the retina was obtained. However, on the day following the vitrectomy, the vitreous was seen to be filled with new greyish flocculent material, also involving the anterior chamber. We again gave intravitreal amphotericin B and ceftazidime. Nevertheless, the eye did not improve. The AC became increasingly filled with exudates. A second vitrectomy was carried out post-operative day 20 with amikacin injected intravitreally. The vitreous cultures came back again with 'no growth'; however, we had reserved a sample for potassium hydroxide (KOH) test for fungal hyphae and for gram stain characteristics. The KOH prep can describe hyphate forms and can give indication of gram polarity.[7] The KOH prep suggested that we were dealing with Gram-positive organisms, although we still had no identification as to the specific organism. A direct Gram stain showed Gram-positive diplococci with a pale connecting band in between, which were identified as *Enterococcus faecium*. Our further research indicated that some strains of this organism were vancomycin resistant (so-called vancomycin-resistant enterococci or VRE) which were only susceptible to certain antibiotics such as

quinupristin-dalfopristin (Synercid), linezolid, daptomycin and tigecycline. [8,9,10,11,12,13] Of all these, only linezolid tablets were immediately available in our country. Linezolid is a synthetic antibiotic, the first of the oxazolidinone class, used for the treatment of infections caused by multi-resistant bacteria including streptococcus, methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE. The drug works by inhibiting the initiation of bacterial protein synthesis. We placed the patient on oral linezolid 600mg BID for the next three weeks. In the meantime, we continued supportive therapy topical dexamethasone, atropine and moxifloxacin. The cornea remained hazy, with blotches of blood on the endothelium. Finally, 28 days after the initial cataract surgery, we were able to obtain and give intravitreal linezolid, which was indicated because the oral form was unable to control the infection. The dosing (200 mcg in 0.1ml) was based on the paper by Antipoli et al.,[14] who had experimented with rabbit eyes. In addition to the linezolid injection, we also gave intravitreal Avastin (bevacizumab) because there were hints of neo-vascularization in the anterior segment.

We saw the patient a week later: the vision had improved somewhat to count fingers at 1 m and the cornea was relatively clear; with the indirect ophthalmoscope, we were able to see the disc and retina. However, a week later, the vision came down again to hand motions. We found the patient had developed a detachment of the retina confined to the posterior pole centered on the macula, confirmed by OCT (Fig. 1). We felt this was an exudative detachment limited to the posterior pole. We gave bevacizumab injection but there was no improvement. At ongoing follow-up, the serous detachment persists. This lack of response to Bevacizumab has been commented on by Chung et al.[15]

3. Discussion

The first case report of endophthalmitis with VRE (*Enterococcus faecium*) was by Bains et al.[11] In addition to intravitreal vancomycin and amikacin, they administered intravenous linezolid 600 mg BID but stopped short of administering the medication into the vitreous. The literature suggests that oral linezolid 600 mg BID is capable of crossing the blood retina barrier.[12,13] We administered oral linezolid for about three weeks, but found it ineffective; clearance of the vitreous haze and opacities. To our knowledge, linezolid has not been given into the vitreous in humans other than in experimental animals.[14,16] In the present case, the eye did not respond to standard antibiotics, vitrectomy, and oral linezolid; the vitreous and anterior chamber cleared only after the injection of intravitreal linezolid in the dose determined from experimental models. After treatment, an OCT revealed persistent serous detachment of the retina in the posterior pole, for which we entertained a differential diagnosis of central serous detachment of the retina.[17,18] It is not clear whether the exudative fluid was linked with the VRE infection, the linezolid injection, other antibacterial, antifungal or periocular steroid injections the patient had, or to the double vitrectomy. Workers have reported persistent sub-macular fluid after vitrectomy.[19–21] So, apart from linezolid, there are several other possible causes for the persistent SRF. In addition, it is important to note that chronic administration of linezolid (5–10 months) has been known to cause reversible optic neuropathy and irreversible peripheral neuropathy.[22,23] The patient did not demonstrate any evidence of these conditions.

4. Conclusions

Endophthalmitis due to vancomycin-resistant enterococci is rare. In the case reported intravitreal linezolid was effective in controlling an *Enterococcus faecium* infection. A persistent exudative detachment of the retina in the posterior pole occurred, of uncertain association with the linezolid therapy.

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Declaration of competing interest

None.

References

1. Hemang K Pandya, Roy Hampton. *Postoperative Endophthalmitis. Medscape. Jan 15*; 2019. Accessed April 2020 https://emedicine.medscape.com/article/1201260-print .
2. Niyadurupola Nuwan, Astbury Nick. Postoperative endophthalmitis. *Community Eye Health*. 2015;28(90):32–33. PMCID: PMC4675262 PMID: 26692647.
3. Endophthalmitis Vitrectomy Study Group. Microbiologic factors and visual outcome in the endophthalmitis vitrectomy study. *Am J Ophthalmol*. 1996 Dec;122(6): 830–846 ([Medline]).
4. Endophthalmitis vitrectomy study. https://clinicaltrials.gov/ct2/show/NCT00000130.
5. Gentile RC, Shukla S, Shah M, et al. Microbiological spectrum and antibiotic sensitivity in endophthalmitis: a 25-year review. *Ophthalmology*. 2014 Aug;121(8): 1634–1642. https://doi.org/10.1016/j.ophtha.2014.02.001. Epub 2014 Apr 2.
6. James Riddell IV, Comer Grant M, Kauffman Carol A. *Treatment of Endogenous Fungal Endophthalmitis: Focus on New Antifungal Agents*. 2011:648–653. CID 2011:52 (1 March) REVIEWS OF ANTI-INFECTIVE AGENTS.
7. Swedish University of Agricultural Science: Veterenary Bacteriology. Information about important bacteria. accessed April 2020 http://www.vetbact.org/index.php?displayextinfo=117.
8. Agudelo Higuita NI, Huycke MM. In: Gilmore MS, Clewell DB, Ike Y, Shankar N, eds. *Enterococci: From Commensals to Leading Causes of Drug Resistant Infection*. Boston: Massachusetts Eye and Ear Infirmary; 2014. PMID 24649504.
9. Gilmore MS, Clewell DB, Ike Y, et al. Enterococcal disease, epidemiology, and implications for treatment. In: Gilmore MS, Clewell DB, Ike Y, eds. *Enterococci: From Commensals to Leading Causes of Drug Resistant Infection*. 2014. PMID 24649504.
10. *"Enterococcal Infections, Vancomycin Resistant" (PDF). Infectious Disease Epidemiology Section Office of Public Health*. Louisiana Dept of Health & Hospitals; 8 September 2008.
11. Harshivinderjit S Bains, David V Weinberg, Robert S Feder, Gary A Noskin. Postoperative vancomycin-resistant Enterococcus faecium endophthalmitis. *Arch Ophthalmol*. 2007;125(9):1292–1293. https://doi.org/10.1001/archopht.125.9.1292.
12. JasonNguyen Mary, Elizabeth Hartnett. Successful management of post-traumatic vancomycin-resistant enterococcus endophthalmitis. *Am J Ophthalmol Case Rep*. April 2017;5:117–118.
13. Fiscella RG, Lai WW, Buerk B, et al. Aqueous and vitreous penetration of linezolid (Zyvox) after oral administration. *Ophthalmology*. 2004 Jun;111(6):1191–1195.
14. Arvin Rolly D Antipolo, Ian P Paredes. Safety of intravitreal linezolid injection: electroretinographic and histopathologic studies in rabbits. *Philippine J Ophthalmol*. October -December 2005;30(4).
15. Chung Y, Seo E, Lew H, et al. Lack of positive effect of intravitreal bevacizumab in central serous chorioretinopathy: meta-analysis and review. *Eye*. 2013;27: 1339–1346. https://doi.org/10.1038/eye.2013.236.
16. Saleh Maher, Lefèvre Sophie, Acar Niyazi, et al. Efficacy of intravitreal administrations of linezolid in an experimental model of S. aureus –related endophthalmitis investigative Ophthalmology and visual science. *Immunol Microbiol*. July 2012;23(8):4331–5094.
17. Moreno-López María, Pérez-López Marta. Pilar Casas-Llera, Elena Jarrín, and Francisco José Muñoz-Negrete Persistent subretinal fluid due to central serous chorioretinopathy after retinal detachment surgery. *Clin Ophthalmol*. 2011;5: 1465–1467.
18. Jia Yu, Xu Gezhi, Chang Qing, et al. Risk factors for persistent or recurrent central serous chorioretinopathy. *J Ophthalmol*. 2019;2019:6. https://doi.org/10.1155/2019/5970659. Article ID 5970659.
19. Abouzeid H, Becker K, Holz FG, Wolfensberger TJ. Submacular fluid after encircling buckle surgery for inferior macula-off retinal detachment in young patients. *Acta Ophthalmol*. 2009;87(1):96–99 [PubMed] [Google Scholar].
20. Seo JH, Woo SJ, Park KH, Yu YS, Chung H. Influence of persistent submacular fluid on visual outcome after successful scleral buckle surgery for macula-off retinal detachment. *Am J Ophthalmol*. 2008;145(5):915–922 ([PubMed] [Google Scholar]).
21. Moreno-López María, Pérez-López Marta. Pilar Casas-Llera, Elena Jarrín, and Francisco José Muñoz-Negrete Persistent subretinal fluid due to central serous chorioretinopathy after retinal detachment surgery. *Clin Ophthalmol*. 2011;5: 1465–1467.
22. Nambiar S, Rellosa N, Wassel RT, et al. Linezolid-associated peripheral and optic neuropathy in children. *Pediatrics*. 2011;127(6). e1528–382. [PubMed] [Google Scholar].
23. Rucker JC, Hamilton SR, Bardenstein D, et al. Linezolid-associated toxic optic neuropathy. *Neurology*. 2006;66(4):595–598 [PubMed] [Google Scholar].