Original Article

Stenotrophomonas maltophilia: An emerging entity for cluster endophthalmitis

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Purpose: This was a study of acute cluster endophthalmitis along with clinical features, culture results, and visual outcomes of 10 eyes of 10 patients after intravitreal injection of Avastin (bevacizumab) in one sitting from a single vial. **Methods:** Retrospective review of intravitreal injection of 1.25 mg/0.05 ml bevacizumab that was given to 10 eyes of 10 patients on the same day from a freshly opened vial. All patients manifested with endophthalmitis the next day. Vitreous tap for direct smear and culture was done. Intravitreal antibiotics and steroids were injected and appropriate treatment begun. The injection vial of the same batch was sent for VITEK™ identification and antimicrobial susceptibility of isolates. **Results:** Endophthalmitis presented within 24 h of intravitreal injection. There was a remarkable absence of posterior pupillary synechia. Two cases were culture-positive (20%), showing pseudomonoid growth. The vial of the same batch revealed a pseudomonoid bacilli *Stenotrophomonas maltophilia* using VITEK™, which was resistant to multiple drugs. Hence, the contaminated vial was identified as the source of infection in our case. Among 10 patients, two underwent pars plana vitrectomy. Visual acuity returned to preendophthalmitis levels in 9/10 eyes after 1 month. One patient was lost to follow-up. Late complications included retinal detachment in one case and neovascular glaucoma in another. **Conclusion:** Early recognition and treatment are key factors in improving outcomes. Causative etiology could be microbial contamination of the drug vial. *S. maltophilia* should be considered a pathogenic organism of postintravitreal endophthalmitis.

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Intravitreal injections are the preferred method of administering drugs for the posterior segment pathologies of eye. It is an invasive procedure and was first described by Rycroft in 1945 when he gave intravitreal injection of penicillin for the treatment of endophthalmitis.[1]

Bevacizumab (AVASTIN®, Genentech, Inc.,) is a 149 kDa full-length humanized monoclonal immunoglobulin G antibody against vascular endothelial growth factor-A (VEGF-A) with a half-life of 9.8 days in human vitreous. It was the first drug therapy approved by the US Food and Drug Administration which could be used to inhibit angiogenesis in tumors such as colorectal cancer.[2] In 2005, Rosenfeld *et al*. first described the use of intravitreal bevacizumab (IVB) for the treatment of macular edema secondary to retinal vein occlusion and exudative age-related macular degeneration (ARMD).[3] The very high cost of other anti-VEGF drugs such as pegaptanib and ranibizumab led to the use of cost-effective bevacizumab in an "off-label" capacity by clinicians worldwide.

Stenotrophomonas (Xanthomonas) maltophilia is an aerobic, nonfermentative, Gram-negative bacillus found in various aquatic environments. It is associated with wet surfaces and can form biofilms in potable water distribution systems. Cells of *S. maltophilia* have the ability to survive with minimal nutrients, for example, in drinking water, treated water (after water treatment of filtration, reverse osmosis, ultraviolet exposure, or deionization), and dialysate effluent.[4] It is a noninvasive, low virulence organism, and frequently colonizes fluids used in a hospital setting (e.g., irrigation solutions, intravenous fluids) and patient secretions (e.g., respiratory secretions, urine, wound exudates). It is usually not capable of causing disease in a healthy host without the assistance of invasive medical devices that bypass normal host defenses.[5]

The first reported case of *S. maltophilia* endophthalmitis was in 1989 after implantation of an intravitreal ganciclovir implant in a patient with acquired immune deficiency syndrome.[6] The risk of cluster endophthalmitis after IVB is high as multiple injections are given from the same vial which is stored at low temperature, or multiple patients may receive injections from the same vial in a single session. The vial sterility is at stake either due to manufacturing protocols, improper storage of drug, or lapse in cold chain. There is no current consensus on the preferred treatment of postinjection endophthalmitis and most clinicians follow the recommendations of endophthalmitis vitrectomy study.

In various clinical trials of anti-VEGF treatment, the reported incidence rate of bacterial endophthalmitis varies between 0.05% and 0.2% per injection, while the incidence of sterile endophthalmitis has been described between 0.09%

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and 1.1% of IVB injections.[7-9] Here, we report the occurrence of endophthalmitis in 10 eyes of 10 patients, after intravitreal injection of bevacizumab from the same vial in a single sitting.

Methods

This study presents a review of 10 eyes of 10 patients who were administered IVB (Avastin®) injection in November 2015 for various posterior segment diseases. It was later approved by the institutional review board.

The mean age of the patients was 55.5 years (range: 45–72). There were five females and five males, six affected in the right eye and four in the left. The details of the procedure and possible complications related to intravitreal injection of bevacizumab were explained to each patient. All patients signed the informed consent forms, in which the use of an off-label drug was also explained. All patients were called in the morning to the operation theater on the same day after preparation with topical antibiotics for 3 days and proper diabetic control. The vial of injection bevacizumab (100 mg/4 ml) came through hospital purchase and was refrigerated at 4°C. The vial was opened on the day of injection in the operation theater, which was maintained with laminar air flow, under full aseptic precautions. The contents of the vial were withdrawn into a 2-ml syringe and then 0.05 ml was transferred into ten, 30 gauge 1 ml tuberculin syringes and each kept on a separate sterile tray. Before the procedure, the operating surgeons scrubbed their hands thoroughly and wore sterile gowns and gloves. Gloves were changed after each injection. The eye of every patient was prepared using standard aseptic procedures. Lids were cleaned with 10% povidone-iodine. An ophthalmic drape and sterile lid speculum were used in each case. Freshly opened 0.5% proparacaine hydrochloride drops were instilled 4–5 times for topical anesthesia. Drops of 5% povidone-iodine were instilled 4–5 times preinjection.

IVB injection (1.25 mg in 0.05 ml) was administered into the vitreous cavity through the inferotemporal quadrant 3.5–4 mm from the limbus by 30-gauge needle attached to a tuberculin syringe. As the needle was withdrawn, a sterile cotton tip was applied for local pressure over the entry site for a few seconds to avoid reflux. Immediately after injection, 5% povidone-iodine solution was applied to the ocular surface. Following injection, the patient's intraocular pressure was checked digitally and fundus was checked to ensure the retinal artery was well perfused. Eye was patched and patient sent home. Oral diamox was administered for 1 day and oral ciprofloxacin was started for 5 days. Topical antibiotic tobramycin and timolol were also prescribed.

Results

All patients came the next morning for routine follow-up in the outpatient department. They all presented with marked diminution of vision, mild pain, redness, vitreous reaction, and hypopyon. All the patients were thoroughly examined using slit-lamp biomicroscopy (SLE), indirect ophthalmoscopy, and B-scan ultrasonography. Patient's clinical symptoms, Snellen visual acuities, and aqueous and vitreous inflammation were graded.

On SLE, all patients had ciliary congestion, cells 3+, flare 2+, 1–2 mm mobile hypopyon. Remarkably, pupillary synechiae were absent. Vitreous exudates were present on B-scan ultrasonography, and fundal glow was present on indirect ophthalmoscopy, but details were not visible in any patient.

All the patients were clinically diagnosed to have postinjection endophthalmitis. They were immediately started on 0.5% moxifloxacin eye drops administered half hourly, and homide eye drops till they were taken up for intravitreal therapy. After taking full aseptic precautions and patient preparation, a vitreous tap along with intravitreal antibiotics and steroid injections was carried out. Vitreous tap was done using a 2-ml syringe and a 26-gauge needle. A minimum of 0.05 ml of vitreous sample was obtained. With a second 1-ml syringe with a 30-gauge needle anterior chamber sample of approximately 0.05 ml was obtained. A small drop of vitreous sample was put onto a glass slide for Gram staining and in another slide for KOH mount, covered by a cover slip. Blood, chocolate, MacConkey, and Sabouraud dextrose agar plates were inoculated and sent to the microbiology laboratory. The same procedure was done for the aqueous sample as well.

Intravitreal injection of vancomycin 1 mg in 0.1 ml, ceftazidime 2.25 mg in 0.1 ml, and dexamethasone 0.4 mg in 0.1 ml were injected. Topical fortified antibiotics (vancomycin 5% and ceftazidime 5%) and cycloplegics (eye ointment atropine sulphate 1%) were started. Intravenous systemic broad-spectrum antibiotics (Augmentin and Amikacin) and oral ciprofloxacin 750 mg BD were also started on the same day. Subconjunctival dexamethasone (0.5 ml) and gentamycin (0.5 ml) BD were also given for 3 days. Patients' blood sugar, kidney function, and liver function tests were also monitored.

There was minimal improvement in all patients the following day. Keeping in mind the early presentation, a presumptive diagnosis of Gram-negative bacillus infective endophthalmitis was made. Intravenous antibiotics were changed to linezolid 600 mg BD and ceftazidime 1 g BD. Oral and topical steroids to reduce the inflammation were also added.

Two patients (2/10) with poor diabetic control deteriorated further and underwent pars plana vitrectomy (PPV) within 48 h. A repeat of the same intravitreal antibiotics and steroids was given to (8/10) patients after 48 h. Three patients showed marked improvement after the second intravitreal, while the other five patients showed a slow response to treatment.

Gram staining showed pus cells in vitreous specimens of five patients, and two cases were culture-positive (20%). Pseudomonoid species was reported in one case and in the other *Providencia alcalifaciens* was cultured, which is also a Gram-negative pseudomonoid. Antibiotic susceptibility testing showed the organisms to be sensitive to ceftazidime, levofloxacin, imipenem, and resistant toward meropenem, amoxicillin-clavulanic acid, clindamycin, and piperacillin-tazobactam.

The vial from the same batch was cultured at our microbiology laboratory and showed Gram-negative bacilli *S. maltophilia* using VITEK™ (automated bacteriological identification system). The organism was found to be sensitive to clindamycin, ceftazidime, cefta-clavulinic acid, and resistant toward meropenem, imipenem, amoxicillin-clavulinic acid, and piperacillin-tazobactam, similar to the reported pseudomonoid bacilli.

By the 6th day, all patients had started showing signs of improvement. However, many patients had epithelial toxicity due to topical medications. Topical vancomycin 5% was stopped and ceftazidime 5% was continued.

All patients were discharged by the 10th day on oral levofloxacin 750 mg, topical antibiotics, cycloplegics, and topical steroids. They were advised to regularly follow-up in the outpatient department.

Visual acuity returned to near preendophthalmitis levels in 9/10 eyes after 1 month. One patient with diabetes who underwent PPV was lost to follow-up (patient no. 5). However, by the end of 2 months, vision of all patients had started deteriorating. One patient with ARMD had retinal detachment which was operated with satisfactory results (patient no. 10). Another patient with central retinal venous occlusion and very poor visual prognosis was advised injection lucentis which he could not afford and went into neovascular glaucoma (patient no. 9). The rest (7/10) were given repeat intravitreal lucentis in the following 12 months and fared well. The mean follow-up period ranged from 6 to 12 months [Table 1].

After noting endophthalmitis, sterilization procedures in the hospital were reviewed. To determine the origin of the infection, multiple surveillance samples were collected from the operation theater air, disinfectants, the povidone-iodine solutions, paracaine, irrigation solutions, syringes and needles, buds, cidex, gauze, and tubes and various instruments. The culture media were incubated for 3 days and were reported to be negative.

Discussion

The incidence of endophthalmitis has risen markedly with the increased use of intravitreal injections in recent times. Multiple large series and population-based studies have reported the per-injection endophthalmitis risk to be 0.03% or less.[10-16] The prospective CATT study has reported endophthalmitis rates of 0.7% with ranibizumab and 1.2% with bevacizumab.[17] The prospective randomized controlled trial of alternative treatments to inhibit VEGF in age-related choroidal neovascularization reported "severe uveitis" in one of 610 patients in 1 year (0.16%), but it did not specifically report endophthalmitis.[18]

McCannell and Moshfeghi *et al*. recently reported eight of 26 (30.8%) and five of seven (71.4%) culture-positive postinjection endophthlamitis cases, respectively, due to streptococcal isolates.[13] Artunay *et al*. have reported two cases of acute culture-positive endophthalmitis per 3022 eyes. *Staphylococcus epidermidis* and *haemophilus influenzae* were isolated and made the incidence of acute culture-positive endophthalmitis 0.066%.[9]

In our report, only two out of ten were culture proven and pseudomonoid species was cultured in both cases. The vial of the same batch was cultured and showed the presence of *S. maltophilia* using VITEK™. Normal culture and identification methods are unable to identify *S. maltophilia* and report it as contaminants or pseudomonoid species. The VITEK™ system gives fast, accurate microbial identification, and antibiotic susceptibility testing. It provides greater automation while increasing safety and eliminating repetitive manual operations and is superior to manual microbial identification techniques.

It is recommended now that the undiluted vitreous and aqueous samples are directly instilled in thioglycollate broth, which is a multipurpose, enriched media, and has the nutrients to support bacterial growth. One drop of the collected sample should also be placed on a glass slide and air-dried before transport for Gram staining. The thioglycollate broth is then centrifuged and the organism-rich supernatant is then plated to get pure colonies without contamination. These colonies can then be identified using VITEK™ or through manual methods.

Horster *et al*. reported an outbreak of *S. maltophilia* endophthalmitis in a series of 26 patients following cataract surgery.[19] In this series, all patients had surgery within 2 days at the same hospital. The irrigation solution was found to be the source of the pathogen. Chang *et al*. and Williams *et al*. reported cases of *S. maltophilia* endophthalmitis after uneventful cataract surgery with intraocular lens implantation. It was related to surgical equipment contamination.[20,21] In 2015, Ji *et al*. reported 14 cases of *S. maltophilia* endophthalmitis in a span of 5 months. The organism was found in cultures of aspiration fluids from phacoemulsification as autoclavable cassettes were used.[22] In our report, the contaminated solution in the vial and the direct injection of the contaminated fluid into the vitreous resulted in quicker and more pronounced inflammation.

S. maltophilia is a multidrug resistance organism due to low-membrane permeability, chromosomally encoded multidrug resistance pumps, plasmids harboring antibiotic resistance genes, and various gene transfer mechanisms involved in the acquisition of antimicrobial resistance. It exhibits intrinsic resistance to a broad range of currently used antibiotics and therefore constitutes a special clinical challenge. It can also develop resistance to a drug to which it was previously sensitive and antimicrobial resistance may emerge during therapy.[4] Our patients responded well after initial topical, systemic and intravitreal ceftazidime injection and the pathogen was sensitive to this drug.

Chen *et al*. and Penland and Wilhelmus reported endophthalmitis with *S. maltophilia* which were resistant to ceftazidime.[23,24] Williams *et al*. reported that two of the three cases of *S. maltophilia* endophthalmitis isolated from culture were resistant to ceftazidime but sensitive to amikacin and ciprofloxacin.[21] In 2015, Ji *et al*. reported resistance to antibiotics such as amikacin, ceftazidime, SMZ/TMP, and ciprofloxacin with sensitivity to levofloxacin.[22] However, recent reports such as those from Chang *et al*. reported sensitivity to ceftazidime, amikacin, polymyxin b, TMP-SMX, ciprofloxacin, and levofloxacin.[20]

The reason for this difference could be due to selective preference of antibiotic use in differing geographic regions or different time periods of study. Furthermore, the methodology, resistance criteria, and media used for antibiotic sensitivities may have differed in these studies. *S. maltophilia* infections can be difficult to treat because of contradictory findings between *in vitro* and *in vivo* antibiotic susceptibility studies. Ceftazidime is often a first-line intravitreal antibiotic agent, chosen because of its wide coverage, and low-intraocular toxicity. Another common first-line option is amikacin. Both drugs produced the described effects in our cases. In our case, the organism was resistant to meropenem, imipenem, amoxicillin-clavulanic acid, and piperacillin-tazobactam.

Table 1: Indication for Avastin therapy and best-corrected visual acuity of patients before intravitreal Avastin injection, best-corrected visual acuity of patients on presentation of endophthalmitis postintravitreal Avastin injection, on subsequent treatment with complications and follow-up

Patient number	Age (years)	Sex	Indication for Avastin injection	BCVA in affected eye pre-injection	BCVA on presentation after intravitreal Avastin injection (day 1)	BCVA (day 2)	BCVA (day 4)	BCVA (day 6)	BCVA (day 10)	Complications	Follow-up period (months)	BCVA at last follow-up
1	50	Male	OS BRVO	20/30	CF at 6 ft	20/200	20/40	20/40	20/40	-	12	20/40
2	57	Female	OS CSME	20/30	CF at 2 ft	FCCF	CF at 6 ft	20/200	20/200	Persistent epithelial defect	6	20/60
3	50	Female	OD BRVO	20/60	HMCF	CF at 3 ft	20/120	20/80	20/80	-	6	20/60
4	45	Female	OD BRVO	20/80	HMCF	FCCF	CF at 6 ft	20/80	20/80	-	12	20/80
5	50	Female	OD DME	20/80	CF at 5 ft	FCCF*	-	-	Lost to follow up	-	-	-
6	68	Male	OD CRVO with ME	20/60	CF at 3 ft	CF at 2 ft	CF at 1 ft	CF at 3 ft	20/200	-	6	20/200
7	60	Female	OD BRVO	20/40	FCCF	HMCF	CF at 2 ft	CF at 2 ft	CF at 5 ft	-	12	20/60
8	50	Male	OS NVD with CSME with PDR	20/60	PL + PR inaccurate	PL + PR accurate*	20/400	20/200	20/200	-	9	20/80
9	72	Male	OD CRVO	CF at 10 ft	HMCF	PL + PR accurate	HMCF	HMCF	CF at 1 ft	Neo vascular glaucoma	12	PL-negative
10	53	Male	OS ARMD	CF at 3 ft	CF at 3 ft	FCCF	HMCF	CF at 1 ft	CF at 1 ft	Retinal detachment	12	FCCF

*PPV done. BRVO: Branch retinal vein occlusion, CSME: Clinically significant macular edema, DME: Diabetic macular edema, NVD: Neovascularization at disc, PDR: Proliferative diabetic retinopathy, ARMD: Age-related macular degeneration, ME: Macular edema, HMCF: Hand movement close to face, CF: Counting fingers, FCCF: Finger counting close to face, BCVA: Best-corrected visual acuity, PPV: Pars plana vitrectomy, OD: Right eye, OS: Left eye, PR: Projection of rays, PL: Perception of light

In our report, endophthalmitis induced by *S. maltophilia* had clinical characteristics similar to those reported by Ji *et al*.[22] Corneal edema was present, but pupil synechia was not seen in these patients at any stage of inflammation. Fibrinolysin, one of the extracellular enzymes of *S. maltophilia*, is said to play a role in inhibiting the process of fibrin membrane and synechiae formation.

Endophthalmitis typically presents after an incubation gap. Only fulminant infections present so early. In our study, the quick presentation was due to the contents of the contaminated vial being directly injected into the vitreous through intravitreal injection. Vitreous is known to be a very good medium for bacterial growth.

The salient features of our report are that endophthalmitis presented within 24 h and treatment started immediately. Intravitreals were given within 3 h of diagnosis. Ceftazidime was used intravitreally, systemically, and topically, to which the organism was later found to be sensitive. Only two patients needed PPV and no patients needed evisceration or enucleation. It is recommended that all patients undergoing intravitreal injections should be followed up the next day. The greatest potential for improvement of outcome lies in early detection and reduction of the time interval between diagnosis and treatment. VITEK™ should be done for all vitreous aspirates for prompt diagnosis.

In our review, all ten patients had signs and symptoms of endophthalmitis, and classically pupillary synechiae were absent at any point. It is possible that this absence could be pathognomonic toward *S. maltophilia* infection. The quick presentation pointed toward Gram-negative infection, but the absence of chemosis, pain, and corneal infiltrate was atypical of a Gram-negative bacteria. *S. maltophilia* is a pseudomonoid whose growth from the injection vial was identified using VITEK™. The manual identification system also revealed pseudomonoid growth from the intravitreal tap thus pointing towards vial contamination. The antibiotic susceptibility profile of both samples is also similar; therefore, the possibility of drug contamination cannot be ruled out.

Many such reports of cluster endophthalmitis due to *S. maltophilia* infection after IVB injection in various parts of the country were published in newspapers from December 2015 to January 2016. The Drug Controller General India (DCGI) banned the drug Avastin for intravitreal use in January 2016. Later, DCGI reversed the ban after various deliberations with retinal surgeons all over India on March 2016, and recommendations were published for the safe and effective use of bevacizumab injection for ophthalmic purpose.[25]

Conclusion

The overall number of patients with endophthalmitis following intravitreal injections has risen dramatically over the past few years. The present report emphasizes the microbial contamination of the drug vial. The message is to stay vigilant and next day follow-up of all patients undergoing intravitreal injections is a must. *S. maltophilia* should be considered a pathogenic organism of postintravitreal endophthalmitis, especially if pupillary synechiae are absent on clinical examination. Its resistance to many drugs commonly used against Gram-negative bacilli and ability to develop resistance during treatment makes it difficult to manage the infection. Early detection with prompt management would improve the visual outcome for these patients. VITEK™ is to be used for early and accurate diagnosis of pathogens.

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Conflicts of interest

There are no conflicts of interest.

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