Global Academic Journal of Medical Sciences

Available online at www.gajrc.com
DOI: 10.36348/gajms.2022.v04i02.002

ISSN: 2706-9036 (P)
ISSN: 2707-2533 (0)

Case Report

A Rare Case of Bilateral Post Intravitreal Avastin Endophthalmitis with Bilateral Good Visual Outcome – A Case Report

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Article History
Received: 13.01.2022
Accepted: 24.02.2022
Published: 04.03.2022

Abstract: This is a case report of post intravitreal injection endophthalmitis encountered at the University Teaching Hospitals–Eye Hospital in Lusaka, Zambia. Endophthalmitis is a clinical diagnosis made when intraocular inflammation involving both the anterior and posterior chambers is attributable to bacterial or fungal infection. Post injection endophthalmitis is a dreaded complication that occurs following intraocular surgery or procedures such as intravitreal administration of anti-vascular endothelial growth factors or corticosteroids. We attended to a rare case of bilateral post intravitreal injection endophthalmitis in a 51- year- old female patient who presented with bilateral severe pain and acute visual loss in both eyes following intravitreal injection of Avastin (bevacizumab) the previous day. On examination, there was severely decreased visual acuity from 6/36 right eye and 6/60 left eye to hand movement in both eyes. There was also corneal haziness, fibrin in the anterior chambers, hypopyon and vitreous cells in both eyes. A clinical diagnosis of bilateral post-injection endophthalmitis was made. There was immediate administration of intravitreal antibiotics of Vancomycin 1.0mg/0.1mL and Ceftazidime 2.25mg/0.1mL with intravitreal Dexamethasone 0.4mg/0.1ml stat dose and systemic ciprofloxacin 750mg 12 hourly for 7 days. Due to prompt diagnosis and treatment vision recovery was excellent in both eyes and both eyes were preserved.

Keywords: Avastin, Endophthalmitis, endophthalmitis.

INTRODUCTION

Endophthalmitis is a purulent intraocular inflammatory response to a bacterial or fungal infection in the eye mostly starting in the aqueous humour, the vitreous body or both [1]. Endophthalmitis is justifiably one of the most devastating and urgent emergencies encountered in ophthalmic practice. Delay in treatment of endophthalmitis may result in permanent vision loss or loss of the eye [1]. There are two types of Endophthalmitis namely exogenous and endogenous. Exogenous endophthalmitis associations include post intravitreal injections, acute postoperative, chronic postoperative, traumatic, filtering bleb-associated, and corneal ulcer [2]. It may be endogenous upon arising from bacteraemic or fungaemic seeding of the eye [2]. Post injection endophthalmitis (PIE) is a dreaded complication which refers to specific endophthalmitis developing following commonly

anti-vascular endothelial growth factors (anti-VEGFs) or corticosteroids [1]. Intravitreal injections have increased in volume worldwide raising the risk of developing endophthalmitis [3].

However, its incidence is very low ranging from 0.016% to 0.09% with the visual prognosis often poor depending primarily on the time to treatment, the virulence of the causative pathogen and the treatment instituted [1,3].

Treatment of PIE must be aggressive and tailored in line the clinical presentation of individual cases. The management of endophthalmitis is guided by presenting visual acuity (VA) and requires prompt administration of intra-ocular antibiotics injection and in some cases a pars plana vitrectomy as well [2,3]. The VA of hand movement (HM) versus light perception (LP) is an essential consideration to be made [4]. Following the endophthalmitis vitrectomy study (EVS) in which a series of 420 patients were reviewed, pars plana vitrectomy was recommended in those with VA of LP whilst local and systemic antibiotics were reserved for those with HM or better even if there seemed to be not significant improvement in VA [4]. Systemic antibiotics are usually poor to penetrate the eye in adequate concentrations though ciprofloxacin and moxifloxacin have shown to penetrate the blood ocular barrier efficiently [4]. Unlike the recommendations of EVS, in today's practice, complete and early vitrectomy for endophthalmitis (CEVE) is being advocated for to foster early recovery for the reasons being dramatic reduction in inflammatory debris, increased retinal oxygenation, reduced risk of retinal necrosis and endophthalmitis maculopathy [5].

Intravitreal corticosteroids are controversial though they are believed to modulate the host inflammatory response to the infection and minimise ocular damage [4]. It should be avoided when a fungal infection is suspected [4]. The most advantageous approach is to simultaneously direct intravitreal treatment towards control of infection and inflammation [6]. Although steroids help in early reduction of the inflammation in exogenous bacterial endophthalmitis, they do not have an independent influence on the final visual outcome [7].

In literature the most common causative organisms of PIE reported are coagulase-negative staphylococci and staphylococcus epidermidis which are fairly abundant in the conjunctival flora of the normal human eye [1, 3, 4]. Second most frequent group of organisms are viridans streptococci an essential part of human oral flora as well [3]. Other causative pathogens involved are staphylococcus aureus, pseudomonas species, Stenotrophomonas Maltophilia and Burkholderia Cepacia [3]. Durand (2013) reported in the study that the most common pathogens in endophthalmitis vary by category [2].

Coagulase-negative staphylococci are the most common causes of post-cataract endophthalmitis while viridans streptococci cause most cases of post-intravitreal anti-VEGF injection endophthalmitis. Bacillus cereus is a major cause of post-traumatic endophthalmitis, and Staphylococcus aureus and streptococci are important causes of endogenous endophthalmitis associated with endocarditis. It was further stipulated that the Gram-positive bacteria cause more than 95% of culture-positive cases. The most commonly isolated organisms in endophthalmitis following intravitreal injections are *Staphylococcus,* 38%–60%, and *Streptococcus* species, 25%–33% [1, 2]. Viridans streptococci (Streptococcus mitis/Streptococcus oralis) also caused an outbreak of 12 cases of postinjection endophthalmitis in Florida, owing to contamination of bevacizumab syringes made up by a single compounding pharmacy [2].

CASE SCENARIO

This is a case of a 51 - year – old female patient from Eastern Province of Zambia. She was a known diabetic mellitus patient for 3 years and had been on oral antihypoglycaemic medications. She was on follow up for bilateral Moderate Non-Proliferative Diabetic Retinopathy with Diabetic Macular Oedema (DME). She had previously received one dose of intravitreal injection of Avastin a month prior to the development of PIE. Having received the second intravitreal Avastin injections in both eyes the previous day, she complained of rapidly diminishing vision, headache and severe pain in both eyes.

The general systemic examination was non-revealing. The best corrected visual acuity (BCVA) was HM in both eyes with intraocular pressures (IOP) of 16 mmHg, right eye (RE) and 15 mmHg, left eye (LE) respectively. Both eyes had corneal haziness whilst the anterior chamber was filled with fibrin and had hypopyon, Figures 1(a) and (b).

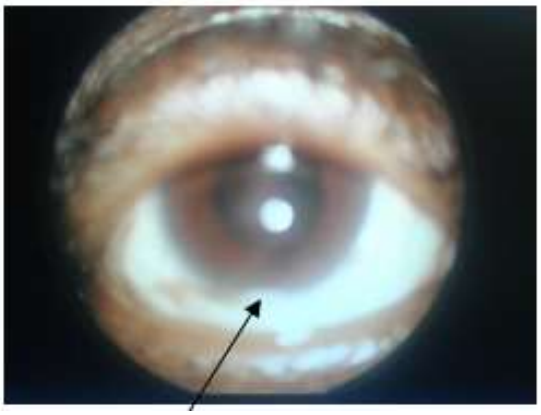

Fig-1(a): RE with streak Hypopyon in the AC

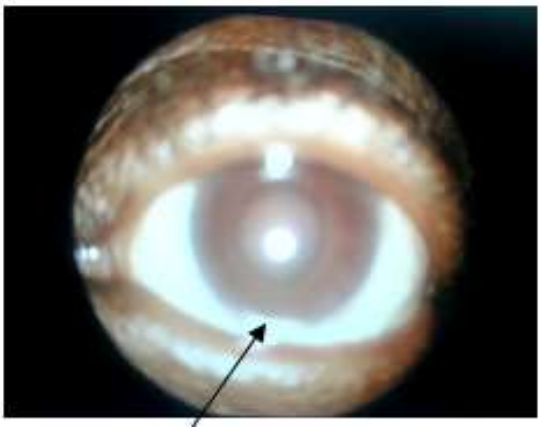

Fig-1(b): LE with streak Hypopyon in the AC

The vitreous was hazy and filled with cells in both eyes. The B-scan ultrasound evaluation performed on both eyes revealed low to medium reflectivity echoes in the vitreous with attached retina in all quadrants of both eyes.

A clinical diagnosis of bilateral post intravitreal injection endophthalmitis was made. In the absence of a recommended vitreous biopsy, bacterial aetiology was presumed based on the timing and presenting features thus prompt empirical antibiotic treatment along with steroids was initiated. She markedly responded to intravitreal vancomycin 1mg/0.1ml, ceftazidime 2.25mg/0.1ml, dexamethasone 0.4mg/0.1ml. She was also commenced on oral ciprofloxacin 750mg 12 hourly for 7 days, topical ofloxacin every 30 minutes, topical prednisolone every two hours and topical cyclopentolate eight hourly.

On first day following the above treatment of PIE, the BCVA improved to 2/60 in both eyes, IOP 13mmHg RE and 12mmHg LE. On subsequent review after one week, her BCVA improved to 6/24 RE and 6/36 LE.

DISCUSSION

Endophthalmitis following intravitreal anti-VEGF injection has characteristics distinct from other types of endophthalmitis [8]. It generally presents earlier, is more likely caused by Streptococcus species and has generally poorer visual outcomes [8]. Labardini and Blumenthal, (2018) reported that most common pathogens included Streptococcus and Staphyloccus species, originating from the patient's, surgeon's or nurse's mouth. In this patient being reported, although a biopsy was not taken bacterial infection was suspected based on the early presentation of less than 24 hours after receiving aliquoted intravitreal Avastin injection. Although biopsy was not taken an investigation to determine the source of infection was done by sending the nine remaining stocks of aliquoted Avastin injection syringes to the University Teaching Hospitals (UTHs) Food and Drug laboratory for microscopy, culture and sensitivity. The results showed that two of the nine samples were contaminated. One sample was positive for staphylococcus aureus coagulase-negative and the second sample was positive for Acinetobacter species. The PIE of the patient could have as a result of one of the two bacteriae isolated.

The breach in asepsis is possible in sterilisation and may lead to loss of aseptic conditions. Several activities or wrong doing may contribute to the causation of PIE. For instance, talking inside the operating room (OR) which could lead to spread of organisms from the oral flora contaminating the environment and leading to drug contamination. Improper scrubbing by surgeon could be another predisposing factor or cause [3]. In this case there could have been a breach in asepsis as was shown by the results from the lab highlighted above.

The most common presentation of PIE is unilateral whilst bilateral involvement is very uncommon. This is explained as in most practice intravitreal injections are not simultaneously performed in both eyes in one sitting for fear of possible infection affecting both eyes. Although same-day bilateral treatment has not been studied in randomized or large controlled trials, the practice is thought to have become more common as it is generally well tolerated and preferred by patients and administrators [9]. The patient under review had same sitting day bilateral treatment which complicated with bilateral PIE. There is no evidence that suggest that bilateral injections reduce the risk of injection associated endophthalmitis. It is imperative that intravitreal treatment of each eye be considered as a separate, sterile procedure,

conducted with caution and without reusing instruments or medications to avoid increasing the risk of bilateral endophthalmitis [10]. In this patient both eyes received Avastin injection on the same day performed by a single surgeon unlike our typical protocol. The infections were given under sterile conditions, but the drug was contaminated.

Clinical presentation usually ranges from 24 hours to 26 days, with the average being four days post injection [3]. Durand (2013) reports that in their study, all the 23 patients with presumed endophthalmitis had pain and vitritis developing one to six days after injection giving an average of 3.4 days and 78% had hypopyon. In a study in England of 47 post-injection endophthalmitis cases found that patients presented an average of 5 days after injection (range: 1–39 days). Our patient was diagnosed with PIE within 24 hours following her second monthly dose of aliquoted intravitreal Avastin to treat DME. In the United Kingdom study, cultures were positive in 60% cases [11] while Labardini and Blumenthal, (2018) demonstrated vitreous cultures in 45%–60% of the cases of infectious endophthalmitis following intravitreal anti-VEGF injection with gram-positive bacteria being responsible for over 95% of culture-positive cases [1]. This finding in the two studies is a clear demonstration of the significance of accurate clinical diagnosis as only a few cases will have positive results confirming the diagnosis. In the case under review, treatment was instituted based on clinical diagnosis.

Clinical signs and symptoms include decreased vision, mild to severe pain, conjunctival congestion, corneal haziness, anterior chamber as well as vitreal inflammation and retina necrosis [1, 3]. In our case, she presented with sudden rapidly diminishing of vision, headache, severe pain and hypopyon in both eyes. While fibrin and the appearance of a hypopyon are primarily associated with infection, non-infectious inflammation cases may also occasionally present with a hypopyon [12].

Empirical antibiotic treatment should be initiated immediately whilst waiting for microbiology reports of vitreous/aqueous samples in order to ascertain the causative microorganism and tailor treatment accordingly [3]. In this case, neither was an anterior chamber nor vitreous tap taken, however management was instituted based on the clinical presentation. The B-scan ultrasound showed bilaterally attached retina in all quadrants and low to medium heterogeneous echoes filling up the vitreous cavity which was suggestive of endophthalmitis. The core treatment options include intravitreal antibiotics or vitrectomy which is reserved for vision of PL [10]. Prompt diagnosis and treatment can save eyes and achieve satisfactory visual results [1]. The patient under review had prompt diagnosis and immediate institution of intravitreal and systemic treatment resulting in saving both eyes. Identifying the infectious agents involved in endophthalmitis is essential to provide the appropriate antibiotic treatment [1].

In many cases, the treated eyes appear worse on day one following treatment before improving subsequently [4]. Sonography typically shows worsening on day one post intravitreal injection a result of the drug reaction in the vitreous hence response to injection on sonography should be assessed on day three at which point a second dose of injection can be considered in the absence of improvement. Albeit the half-life of the drug has to be taken into consideration as a guide for re-injection with most antibiotics ranging between 24-72 hours and antifungals up to one week [13]. We observed remarkable improvement in her vision and clinical picture on day one following intravitreal injections of Vancomycin, Ceftazidine and Dexamethasone. Intravitreal dexamethasone does not seem to have any detrimental effect on the efficacy and potency of the intravitreal antibiotics and a dose of 400µg is non-toxic to the retina. Doses higher than 800µg are known to cause vacuolation between the outer plexiform and outer nuclear layers and the primary site of toxic reaction is the Müller cells [14]. In our case intravitreal dexamethasone worked very well and was cardinal in improving the patient's condition clinically and in terms of vision.

The Endophthalmitis Vitrectomy Study (EVS) protocol recommended reinjection if the infection was worsening at 36-60 hours after initial injection [4]. Patients with no culture growth, equivocal growth, or coagulase-negative staphylococcus had a 5% rate of additional procedures, compared to 30% in patients with cultures that grew gram negative or other gram positive organisms [4]. On subsequent follow up, our patient continued to show great improvement and reinjection was not necessary.

Okada *et al*., (1994) looked at endogenous endophthalmitis and showed that the outcomes and risk factors for poor visual outcomes were most commonly attributed to virulence of the offending organism, endophthalmitis maculopathy, older age, Diabetes Mellitus, low or high IOP [15]. Despite having underlying Diabetes Mellitus with DME the case under review responded well to the timely

treatment of antibiotics and steroids. Multiple strategies have emerged to reduce the risk of endophthalmitis after anti-VEGF injections. We can minimize the risk by applying established guidelines for injection despite the current possibility not to eliminate the risk, which should not be considered a "never event" [8]. However, prevention of endophthalmitis involves thorough preoperative screening, control of risk factors like localised adnexal infection or systemic condition [3]. So far, no study has shown evidence that prophylactic topical antibiotics reduces the risk of post injection endophthalmitis [16].

Evidence has shown that topical povidone-iodine is the most effective protective-prophylactic measure aimed at reducing the incidence of bacterial infection following intravitreal injections [1, 3, 8, 10]. Several groups have reported that the application of povidone-iodine after placing the lid speculum decreases the incidence of PIE due to the prevention of contact between the eyelid and the injection site [1, 8, 10]. Maintenance of drug cold chain protocols is also vital in preventing PIE. The process of aliquoting intravitreal drugs must be performed under sterile conditions, and there should be a regular check of contamination by sending the drugs for microbial cultures [2]. Intraoperative measures include discouragement of bilateral injections [3, 10]. Lau *et al*., (2018) in their review article reported that the 1/1,111 risk of endophthalmitis was based on a unilateral injection while the bilateral case is therefore unlikely to have such low risks [10]. It is therefore important to consider the local protocol or surgeon's discretion such as two injections to be performed between a few days to one week apart. In this case, bilateral intravitreal injections were given on the same sitting.

Additional measures include proper OR sterilisation such as fumigation, swabbing the OR and sending the specimens for microscopy, culture and sensitivity. The OR floors should be cleaned with Hydrogen peroxide (H_2O_2) solution (diluted) and walls cleaned with alcohol-based solutions, the combination of glutaraldehyde and formaldehyde (such as Bacillol) as per World Health Organisation (WHO) recommendations [3,10].

CONCLUSION

Timely management with intravitreal injections of antibiotics is vital in restoring vision in order to prevent blindness and loss of the eye or eyes. Intravitreal steroids can play a vital role in reducing the inflammatory response thus protective of tissue damage but the usage is limited to bacterial endophthalmitis only. Prompt and aggressive treatment must be patient-tailored depending upon the clinical presentation as the prognosis is directly related to the presenting visual acuity, offending organism and the systemic status of the patient.

DECLARATION OF PATIENT CONSENT

The authors indicate that appropriate consent forms were obtained from the patient. In the forms the patient gave consent of her images obtained and the clinical information to be published. The patient understands that their full names and initials will not be used for publication in the journal and that due effort will be made to conceal their identity but anonymity cannot be guaranteed.

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