Hydrophilic Lens Opacification after Intravitreal Anti-VEGF Injections: A Case Series

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Keywords
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Abstract
Our objective in this retrospective case series was to report 4 cases of hydrophilic intraocular lens (IOL) opacifications after repeated intravitreal bevacizumab injections. This is a retrospective analysis of all the cases of IOL opacifications presenting to a tertiary referral ophthalmic center in Beirut between January 2013 and January 2019. Four cases were included in the study, of which one was treated for vitreal hemorrhage, the other for macular edema secondary to wet age-related macular edema, and the rest for macular edema secondary to diabetic retinopathy. The mean age of the patients was 71 years with a male predominance and a mean of 5 injections. The IOL opacifications appeared approximately 24 months after first bevacizumab injection. The opacification could be explained by multiple theories such as a possible anterior or posterior segment subclinical inflammation secondary to intraocular interventions, interaction between the hydrophilic properties of the IOLs and anti-vascular endothelial growth factor injection's content, impurities transmission during injection, or faulty IOL manufacturing.

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Introduction

Bevacizumab (Avastin®) is a full-length, humanized monoclonal antibody directed against all the biologically active isoforms of vascular endothelial growth factor (VEGF-A) [1]. Bevacizumab was primarily developed for the treatment of a variety of solid tumors [1]. Though it was not formally studied or approved for any intraocular disease, Rosenfeld's pioneering work and the unavailability of a related ocular drug, ranibizumab, led to rapid and wide use of bevacizumab all over the world [1]. Intravitreal bevacizumab is used for many pathologies including proliferative diabetic retinopathy, wet age-related macular degeneration (ARMD), retinopathy of prematurity, retinal vein occlusions, and many more [2]. Many documented side effects exist. Ocular side effects range from a subconjunctival hemorrhage to a tractional retinal detachment, in addition to some systemic side effects, such as a decline in kidney function [2]. Hydrophilic intraocular lenses (IOLs) have well been documented to undergo calcification after implantation during cataract surgery in some cases. This phenomenon has been studied and many theories have tried to explain the etiology behind it. While some studies have linked this complication to intravitreal rTPA injection [3], others have postulated that inflammation post-intraocular interventions may be causative, and it was not until the year 2018 that Roland et al. [4] have reported this complication in two eyes following intravitreal anti-VEGF injections [5]. The following year saw a group led by Balendirian et al. [5] linking hydrophilic IOL calcifications to posterior segment procedures [4]. The aim of this study is to highlight 4 cases of IOL anterior surface opacification after repeated intravitreal injections of bevacizumab.

Methods

The charts of all the cases of IOL opacifications presenting to a tertiary referral ophthalmic center in Beirut from January 2013 to January 2019 were retrospectively reviewed. Cases found to have undergone intravitreal injection of bevacizumab after cataract surgery were included in the study. Intravitreal injections (1.25 mg/0.05 mL) were given on PRN basis according to fundoscopic and OCT findings. All injections were performed by the same ophthalmologist (E.W.) under sterile conditions 4 mm from the limbus superiorly. Cases of IOL pitting secondary to YAG laser capsulotomy were excluded from the study. A statement of consent to publish findings and slit-lamp photos was gathered from all patients.

Results and Case Presentations

Four patients were included in the study. Of these, one was treated for recurrent vitreal hemorrhage, one for macular edema secondary to wet ARMD, and the rest for macular edema secondary to diabetic retinopathy. The mean age of the patients was 71 years with a male predominance at 3:1 male to female ratio and a mean of 5 injections. The IOL opacifications were noted after approximately 24 months after the first bevacizumab injection. All opacifications shared similar features such as white granular crystalline appearance, IOL anterior surface involvement, and microscopic vacuole-like appearance on retro illumination (shown in Fig. 1, 2). All IOLs were hydrophilic from the same manufacturer (Rayner Superflex 620H). None of the patients had undergone any previous vitrectomy or YAG laser capsulotomy. None of the IOLs were explanted.
**Case Presentations**

**Case 1**
A 63-year-old female patient was known to have diabetes mellitus type 2, hypertension, dyslipidemia, and diabetic maculopathy. She underwent an uneventful cataract surgery (OD) in October 2015; a clear IOL (Rayner Superflex 620H, hydrophilic) was placed. After 3 months, patient developed a vitreal hemorrhage (OD) as a complication of her diabetic retinopathy and was started on bevacizumab injections. A total of 4 injections were performed before the opacifications were noted; intervals of injections were 4 months, 10 months, and 10 months, respectively. During this period, no complications were reported or addressed.

**Case 2**
A 73-year-old male patient was known to have hypertension, diabetes mellitus type 2, and dyslipidemia. He underwent an uneventful cataract surgery (OS) in June 2013 with insertion of a clear IOL (Rayner Superflex 620H, hydrophilic). The patient was found to have macular edema secondary to diabetic retinopathy and was started on bevacizumab injections. A total of 7 injections with a mean interval of 3 months were performed before the opacifications appeared (shown in Fig. 1). During this period, no complications were reported or addressed.
Case 3

An 83-year-old male patient was known to have hypertension and ARMD. He underwent uneventful cataract surgery (OD) in October 2016 with insertion of a clear IOL (Rayner Superflex 620H, hydrophilic). The patient received a total of 4 injections of bevacizumab for macular edema secondary to wet ARMD, with an interval of 8 months, 5 months, and 1 year, respectively, before the opacifications appeared (shown in Fig. 2). During this period, no complications were reported or addressed.

Case 4

A 66-year-old male patient was known to have diabetes mellitus type 2 and dyslipidemia. He underwent uneventful cataract surgery (OS) in November 2015 with insertion of a clear IOL (Rayner Superflex 620H, hydrophilic). The patient received a total of 5 injections of bevacizumab for macular edema secondary to diabetic retinopathy before the opacifications appeared. Intervals of injections were 3 months, 4 months, 1 year, 4 months, and 4 months, respectively. During this period, no complications were reported or addressed.

Discussion

Intravitreal bevacizumab is being widely used for intraocular neovascular disorders and macular edema [6]. Its toxicity has been studied with a greater interest to its effect on the retina [7]. This paper discusses intravitreal anti-VEGF injections and more specifically bevacizumab injections as a possible etiology for the observed hydrophilic IOL opacifications. We report a series of 4 patients having anterior IOL opacifications following bevacizumab intravitreal injections.

The large disparity in the presentation of IOL opacification could suggest multiple etiologies for this phenomenon [8]. It may include formation of opacifications/precipitates on the IOL surface or within the IOL substance; opacification by excess influx of water in hydrophobic materials; direct discoloration by capsular dyes or medications; coating by substances such as ophthalmic ointment and silicone oil; and slow, progressive degradation of the IOL biomaterial [8, 9]. Recently, a new classification is proposed regarding the causes of IOL calcification: primary that is IOL related and secondary that is resultant from environmental circumstances such as preexisting disease and false positive where other disease is misdiagnosed as calcification [8]. Through our case report, having all 4 patients having the same norms as a basis to exclude any bias and false positives, all 4 patients have the same IOL implants, same intravitreal dosage of 1.25 mg/0.05 mL bevacizumab, and no other associated complications were reported.

All patients were observed throughout their treatment regularly. Through their follow-up, we started noticing the emergence of new opacifications/precipitates on the anterior IOL surfaces. Having in our database a large number of patients with many intravitreal injections of bevacizumab, only patients having IOL the specific type of hydrophilic IOL (Rayner Superflex 620H®) were noted to develop IOL opacifications. To note, the emergence of the opacifications occurred earlier in patients that received a greater number of injections. Thus, a direct relationship may be correlated between the two. Many explanations can be drawn to justify these findings.

Our first plausible explanation is that posterior segment procedures, in our cases an intravitreal anti-VEGF injection, could be the cause of the calcifications. This theory has been supported by Balendiran et al. [5] who studied thirty hydrophilic acrylic IOLs that were explanted due to opacification after diverse posterior segment procedures, which were 3 cases of anti-VEGF injection. Their work led to the postulation that any subsequent and
repeated intraocular intervention after a hydrophilic acrylic IOL implantation increases the risk of calcium deposition on the lens. This theory aligns with our findings that a greater number of repeated injections resulted in earlier opacification.

Their multinational study led to the conclusion that different posterior segment interventions causing similar patterns of IOL calcification can be explained by resultant chronic subclinical inflammatory changes extending to the anterior segment and molecular changes due to blood-aqueous barrier breakdown [5, 10]. The posterior aspect of our IOLs was spared from the calcifications which may be explained by the cover provided from the intact posterior capsule.

Hydrophilic IOLs have been reported to develop opacification with vacuole-like appearance related to material impurities, faulty storage, and defective manufacturing without reference to any ocular intervention after implantation [11, 12]. In view of the fact that the reported cataract surgeries were performed in the same hospital, years apart, with IOLs originating from different batches, we believe such risk factors are less fitted explanations to the findings in our case series. Likewise, intravitreal bevacizumab injections are prepared and compounded by in-house pharmacies with multiple separate doses originating from the same vial, posing a great risk to preparation sterility and impurities transmission [13].

One impurity of pertinent significance to our case series is air. It has been noted that some anterior and posterior segment procedures, namely, Descemet-stripping automated endothelial keratoplasty/Descemet membrane endothelial keratoplasty, where air or gas is left with direct contact to the anterior or posterior surface of the implanted lens could be related to the formation of the described opacifications [14, 15].

Furthermore, a possible molecular interaction between the IOL and injection’s content could have led to the formation of the reported deposits. The Rayner Superflex 620H® and the bevacizumab molecule along with its dissolving solution are hydrophilic. The anti-VEGF storing solution contains a buffer solution along with a sugar source and an emulsifier, whereas that of the aqueous solution contains variable minerals including sodium, calcium, and potassium that may interact with the storing solution after several injections and forming considerable amount of precipitation that may lodge on the IOL. The emulsifier in which the bevacizumab storing solution contains the hydrophobic compound is polysorbate 20. Once injected in the vitreous, a possible dissociation may have occurred between the bevacizumab’s active ingredient and polysorbate causing the polysorbate to be nonhomogeneous with the hydrophilic environment in the vitreous and forming an IOL deposit.

In conclusion, our small case series correlates intravitreal anti-VEGF injections with Rayner Superflex 20 hydrophilic IOL calcification between hydrophilics. The relationship between posterior segment interventions, in particular anti-VEGF injections, and hydrophilic IOL calcification yields a promising subject for further research but nonetheless requires further data and investigations to demonstrate a causal relationship. Ophthalmologists should be alert about the possibility of hydrophilic IOL opacifications after intravitreal injection of bevacizumab in pseudophakic patients.

**Statement of Ethics**

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from participants for publication of the details of their medical case and accompanying images. This study protocol was reviewed and approved by the University of Balamand Institutional Review Board with the following reference number: AEC210209003.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.W. drafted the introduction and literature review. Participated in alignment and revision of the manuscript.

K.S. carried out data collection and contributed to the drafting and revision of the manuscript.

J.A. drafted and revised the results and discussion and carried out the statistical analysis.

F.S. participated in the study and its methods' design; coordinated the drafting of the manuscript; and contributed to the statistics and data collection and analysis.

E.L.W. conceived the study and assisted in its design and contributed in data collection and optimization.

All authors read and approved the final manuscript.

Data Availability Statement

All data used for writing this paper are found in journals with access granted to readers. References are listed below.

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