A Novel Application of Anterior Chamber Cells and Aqueous Humor Cytokines Analysis in Uveitis-Glaucoma-Hyphema (UGH) Syndrome: A Case Report

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Abstract

Background: Uveitis-glaucoma-hyphema (UGH) syndrome could be identified by clinical history and detailed ophthalmologic examination. In order to better understand the pathological processes of UGH syndrome, we introduced findings of enhanced red blood cells (RBCs) and inflammatory factors expression in a case of an UGH syndrome.

Case presentation: A 51-year-old male was presented to the eye clinic due to right reduced visual acuity, eye redness and pain. There was a history of implantation of intraocular lens (IOL) 8 years ago in the right eye. Ophthalmic examination revealed the best corrected visual acuity of 60/100 (0.25/-1.25×7), intraocular pressure (IOP) of 39.7 mmHg, and under natural pupils, the IOL remained centered. After full mydriasis of the right eye, slit lamp examination showed that the superior temporal haptic of the IOL was located outside the anterior capsule, and ultrasound biomicroscopy (UBM) showed the contact and continuous mechanical chaffing between IOL and iris. But, in this case report, there was no typical anterior chamber (AC) hemorrhages under the slit lamp, so we performed aqueous humor (AH) cytokines and AC cells analysis. AH smear showed RBCs, which confirmed that the AC cells seen under slit lamp were RBCs. Flow cytometry cell-based assay showed a significantly elevated concentrations of interleukins 6, 8 (IL-6, IL-8), adhesion molecules (vascular cell adhesion molecule, VCAM), and basic fibroblast growth factors. The existing IOL was readjusted. After the surgery, the patient had resolution of AC inflammation. Uncorrected visual acuity of the right eye was 20/20. The IOL was described as centered in-the-bag and UBM showed there was no contact between IOL and the posterior surface of the iris. The IOP was 16mmHg OD without IOP lowering medications.

Conclusions: AH cytokines and AC cells analysis can effectively assist in the differential diagnosis and treatment of UGH syndrome and provides laboratory basis.
**Introduction**

Uveitis-glaucoma-hyphema (UGH) syndrome is a triad characterized by recurrent episodes of elevated intraocular pressure (IOP), anterior chamber (AC) hemorrhages, AC inflammation, and blurred vision. UGH syndrome or Ellingson’s syndrome was first described in 1978, and it is generally associated with contact between a malpositioned AC intraocular lens (IOL) and the iris or ciliary body, leading to mechanical tissue trauma [1,2]. UGH syndrome is a severe complication of cataract extraction and a cause for blurry vision weeks to months after surgery. Currently, with the upgrades in lens design, surgical techniques, and the IOL is implanted into the capsular bag, minimizing the possibility of the IOL contacting the uvea and reducing the incidence of UGH syndrome (from 2.2-3 to 0.4-1.2%) [3-5].

In the report, we present an application of aqueous humor (AH) cytokines and AC cells analysis in a case of an UGH. Ethical approval for this study was provided by the Ethics Committee of affiliated eye hospital of Shandong University of Traditional Chinese Medicine and written informed consent was obtained from the patient. The study and data collection conformed with the principles of the Declaration of Helsinki. Informed consent was obtained from the patient for the publication of this study.

**Case presentation**

**Participants**

A 51-year-old male was presented to the affiliated ophthalmic hospital of Shandong university of Traditional Chinese Medicine, Jinan, China in June 2021 due to right reduced visual acuity, eye redness and pain that had repeatedly appeared in the past 8 years, and the symptoms were aggravated for 2 days. The patient reported that he had undergone uneventful phacoemulsification with implantation of a posterior chamber in-the-bag ReSTOR multifocal lenses (model SN6AD1, Alcon Laboratories, Inc., Fort Worth, TX, USA) in his right eye in 2013 at his local hospital, 8 years before presentation. The patient repeatedly presented with decrease of visual acuity, eye redness in the right eye after surgery. He was diagnosed as uveitis at other hospitals and the symptoms improved slightly after hormone treatment. Six years later (2019 year), a cataract surgery was performed on his left eye. A history of head injury caused by tricycle for 19 years was reported.

**Ocular examinations**

After careful review of his medical history, a series of detailed ophthalmic examinations were conducted. The visual acuity of 40/100 and the best corrected visual acuity was 60/100 (-0.25/1.25×7) in the right eye. The visual acuity of the left eye was 20/20. Intraocular pressure (IOP) was 39.7 mmHg OD and 13 mmHg OS.

Slit lamp examination in the right eye showed a clear cornea, diffuse pigmented keratic precipitates, flare in AC (++) and under natural pupils, the IOL remained centered. The pupils were round of about 3.5 mm in diameter and pupillary margin organized membrane. He was found to have 2+ AC cells and his AC showed no evidence of hypopyon or hyphema on OD (Figure 1A, B). Slit lamp did not detect any abnormality in the left eye (Figure 1C). Gonioscopy further revealed all the AC angles were open and pigmentation in the trabecular meshwork of the two eyes, with OD
and II OS (Figure 1D, E). Funduscopic examination revealed a vertical cup disc ratio of 0.5 in the right eye. There was no abnormality in the left eye (Figure 2A). B-scan ultrasound showed an inhomogeneous weak dough like echoes throughout the vitreous cavity of the right eye (Figure 2B). Automated visual field examination showed the arcuate scotomas in the superior quadrant in right eye. Left eye was approximately normal (Figure 2C). Considering that the patient has undergone IOL implantation, a possible diagnosis of UGH syndrome was proposed. After dilation of the pupil, we double checked the eyes by slit lamp (Figure 3). The superior temporal haptic of the right IOL was located outside the anterior capsule bag, and the inferior nasal haptic of the IOL was located in-the-bag.

Ultrasound biomicroscopy (UBM) showed the chafing between the IOL and the posterior surface of the iris at 10-o’clock position (Figure 4A). Chafing of the posterior iris by the IOL haptic almost confirmed the diagnosis of UGH syndrome. It was also necessary to confirm that the AC cells seen under slit lamp were red blood cells (RBCs).

**Surgery and AH Analysis**

Considering that the patient was implanted with multifocal IOL and most of the lens capsule was complete. The optimal treatment modality is to rotate the existing IOL and adjust it into the capsule bag to remove the chafing between IOL and iris. AH samples (100 to 150 µl) were collected at the beginning of the surgery. Before making the incision, a paracentesis was carried out at the limbal region using a 1 ml graduated syringe. No bleeding and contact with peripheral tissue during puncture. AC cells were detected by AH smear (Giemsa stain). The specific operation is as Kalogeropoulos CD’s description [6]. The RBCs in the AH were identified (Figure 5). Cytokines were detected by flow cytometry cell-based assay. Our findings showed a significantly elevated concentrations of interleukins 6, 8 (IL-6, IL-8), adhesion molecules (vascular cell adhesion molecule, VCAM), and basic fibroblast growth factors (BFGF) (Table 1). The AC RBCs, AH cytokines, high IOP, and dynamic interactions between IOL and iris determine a diagnosis of UGH syndrome.

**Follow-up**

The patient had resolution of AC inflammation after surgery (Figure 6A, B). UCVA was 20/20 OD. The IOL was described as centered in-the-bag and UBM showed there was no contact between IOL and the posterior surface of the iris (Figure 6C). The IOP was 16mmHg OD without IOP lowering medications.

**Discussion and conclusions**

UGH syndrome is usually an iatrogenic disease. It was initially described in 1978 as a complication of intraocular friction caused by first generation AC IOL [7]. It has also been found more recently in subjects submitted to cataract surgery and IOL implantation (either in the sulcus or in-the-bag) [8]. It is noteworthy that a UGH syndrome could occur even the IOL remained centered without dislocation in the state of small pupil. Generally, the clinical signs and symptoms of these patients were frequently mild in this situa-
tion. In this case report, under natural pupils, slit lamp shows that the IOL remained centered. After full mydriasis, the dislocation of the haptic of the IOL can be seen. The cause of UGH syndrome in-the-bag IOL is due to large capsulorhexis, the haptics were not in the capsular bag. The persistent mechanical chaffing between IOL and iris leads to the spread of iris pigment and the disruption of blood-aqueous barrier, resulting in the triad of intraocular inflammatory reaction, elevated IOP and AC hemorrhages. Cytokines trigger and boosts the inflammatory responses in which complement and fibrin enter the eye and are activated by the surface of the IOL [9]. In our case study, this was evidenced by the organized membrane of the pupil margin. Elevated IOP can be caused by direct mechanical injury, with clogging of the trabecular meshwork by pigment or scarring, or by the inflammatory reaction itself.

For ocular lesions with inflammatory compound, the analysis of cytokines in AH has become extremely attractive for research [10-13]. However, the expression of inflammatory cytokines in UGH syndrome has not been reported previously. In this case report, IL-6, IL-8, VCAM and BFGF concentrations were significantly elevated. BFGF is a member of a family of heparin-binding growth factors. It is found in normal tissue associated with heparan sulfate on the cell surface or extracellular matrix. It has been shown that BFGF accelerates the rate of wound closure by increasing cell proliferation, promoting tissue angiogenesis, and inhibiting myofibroblast differentiation [14]. Gallego-Muñoz et al [15] showed that upon adding TGF-β1 and BFGF to the culture medium of human corneal fibroblasts, the cellular proliferation process is strengthened and the myofibroblast differentiation and cellular migration are remarkably reduced, with TGF-β1 treatment alone comparison. In addition, at sites of inflammation, BFGF is released and upregulated by the action of proteases and heparinases [16]. The increased levels of BFGF are directly related to the formation of pupillary margin organized membrane, and the increased levels of BFGF also indicates the presence of inflammatory reaction. VCAM an endothelial receptor belonging to the immunoglobulin superfamily is associated with the disruption of the blood-ocular barrier [17]. IL-6 is an interleukin that acts as a proinflammatory cytokine. It is secreted by macrophages, monocytes and T and B cells to stimulate an immune response during tissue damage. Previous investigations suggested that IL-6 mediates the inflammatory processes and immune responses in many eye diseases such as, Behcet’s disease [18], and pseudoexfoliation glaucoma [19]. IL-6 is involved in vascular hyperpermeability and endothelial barrier dysfunction [20,21]. This suggests a possible involvement of elevated IL-6 levels in the active intraocular inflammation and break down of the blood–aqueous barrier. IL8 is an important neutrophil chemotactic factor, which plays a key role in the defense mechanism through its effects on neutrophil activities [19,22]. Previous studies of inflammatory eye disease [23,24] have showed that increased levels of IL-6 and IL-8 were associated with intraocular inflammation. We found similar changes among these cytokines in the samples from current UGH patients in the present study. The increased levels of the IL-6, 8 and BFGF suggested active intraocular inflammation.

The treatment of UGH syndrome depends on the clinical signs, symptoms, and disease severity, and to a lesser extent on the type and position of IOL. In the mild-to-moderate cases, treatment with a combination of anti-inflammatory and anti-glaucoma medications might be sufficient. However, for recurrent patients, the fundamental treatment is to eliminate the persistent mechanical chaffing between IOL and iris and/or ciliary body. For advanced cases, surgical intervention may be the only option, usually with a complete IOL repositioning or exchange [25-27]. The technologies of IOL repositioning depends strongly on the severity of adhesion formation between the IOL and the capsular bag. In future cataract surgery, it is very important to implant IOL in the capsular bag, not ciliary sulcus, with circumferential overlapping of the appropriately-sized anterior capsule over the optic edges of IOL to reduce UGH morbidity [28]. In conclusion, medical history, a necessary UBM, along with a proper assessment of the IOL position were necessary for early diagnosis of UGH. AH cytokines and AC cells analysis, may offer more useful information for correct diagnosis of UGH and provide the corresponding laboratory basis [29-31].

Declarations

**Ethics approval and consent to participate:** This study complied with the tenets of the Declaration of Helsinki. Ethics approval was not required for the reason that this was a single case report.

**Consent for publication:** The written consent obtained from the patient for any personal or clinical details along with any identifying images to publish in this report. The copy of the written consent form is available for review by the journal Editor.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article.

**Competing Interest:** All authors declare that they have no conflicts of interest.

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**Authors’ contributions:** Xiujuan Du and Xiuyan Zhang were the major contributors to the drafting of the manuscript. Fang Sha and Haifeng Ji collected the ophthalmological data. Dongmei Liu and Yan Liu interpreted the ophthalmological data. The corresponding authors reviewed and approved the final manuscript.

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**Keywords:** Bladder cancer; Machine learning; Neoadjuvant chemotherapy; Prediction model.

**Abbreviations:** UGH: Uveitis-Glaucoma-Hyphema; RBCs: Red Blood Cells; IOL: Intraocular Lens; IOP: Intraocular Pressure; UBM: Ultrasound Biomicroscopy; AC: Anterior Chamber; AH: Aqueous Humor; IL-6: Interleukins 6; IL-8: Interleukins 8; VCAM: Vascular Cell Adhesion Molecule; BFGF: Basic Fibroblast Growth Factors.

**References**


