Anterior chamber fibrinoid syndrome after cataract extraction in a patient on ibrutinib for B-cell chronic lymphocytic leukemia: a case report and review of the literature

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Abstract

Background: Ibrutinib is a tyrosine kinase inhibitor commonly used in patients with chronic lymphocytic leukemia. Based on the published literature, it has a very sound ophthalmologic safety profile. In the following, we describe a case of anterior chamber fibrinoid syndrome in a patient on ibrutinib for B-cell chronic lymphocytic leukemia after uncomplicated cataract extraction.

Case presentation: A 75-year-old white man with B-cell chronic lymphocytic leukemia on ibrutinib therapy and without significant past ocular history presented 1 day after uncomplicated phacoemulsification with in-the-bag intraocular lens implantation with multiple, discrete, pigmented cords in the anterior chamber. His vision was 20/100 and intraocular pressure was 43 mmHg. There was no hypopyon, hyphema, or cellular reaction. The dilated fundus examination was unremarkable. He was diagnosed as having fibrinoid syndrome and started on topical prednisolone, brimonidine, timolol-dorzolamide, and orally administered acetazolamide. Within 2 weeks, the fibrin cords disappeared completely, vision improved to 20/30, and the intraocular pressure normalized off all medications.

Conclusions: The precise etiology of fibrinoid syndrome remains unclear. This is the first case of fibrinoid syndrome in a patient on ibrutinib, which is known to cross the blood–brain barrier and induce intraocular changes. It is important to differentiate this syndrome from toxic anterior segment syndrome and endophthalmitis, and to initiate appropriate treatment. The fibrin bands tend to be exquisitely sensitive to topical steroids and to resolve within a few weeks without sequelae.

Keywords: Fibrinoid syndrome, Fibrinoid reaction, Anterior chamber, Phacoemulsification, Ibrutinib, Chronic lymphocytic leukemia

Background

Fibrinoid syndrome was a term first used by Sebestyen in 1982 to refer to patients with proliferative diabetic retinopathy (PDR) who developed thick transvitreal or retropupillary fibrin bands or cords in the vitreous cavity after undergoing multiple surgical procedures for diabetic sequelae [1]. It may result in complications and poor visual outcome despite the use of topical and systemic steroids. A similar constellation of clinical findings was attributed to extensive cryotherapy by Machemer in 1975 and to hypotony by Schepens in 1981 [2, 3].

The signs of fibrin or fibrinoid reaction can range from the presence of a few fibrin strands to a dense pupillary membrane in the anterior chamber [4]. It is most commonly associated with diabetes, pseudoexfoliation, glaucoma, and extracapsular cataract extraction (ECCE) [5]. It typically presents within 1–2 weeks after surgery, lasts up to 3–4 weeks, and resolves completely without permanent sequelae after initiation of topical steroid therapy.
Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase that is commonly used in the management of patients with chronic lymphocytic leukemia (CLL) [6]. It is known to cross the blood–brain barrier (BBB) and is able to gain access to and affect the anterior chamber based on preclinical studies and clinical reports [7–10].

Case presentation
A 75-year-old white man presented 1 day after uncomplicated phacoemulsification and in-the-bag intraocular lens (IOL) implantation with multiple, intertwined, discrete, pigmented cords in the anterior chamber (Fig. 1a). The fellow eye was phakic with best-corrected vision of 20/30 and had not undergone any prior surgeries/procedures. He did not have a history of diabetes, glaucoma, uveitis, trauma, or other intraocular surgery. Past medical history was significant for atrial fibrillation, Raynaud’s syndrome, and B-cell CLL previously treated initially with rituximab and chlorambucil, and more recently with ibrutinib for 6 months prior to cataract extraction. The lens had 2–3+ nuclear sclerosis without pseudoxfoliation or phacodonesis, and did not require mechanical pupil expansion. A retrobulbar block of 2% lidocaine and 0.75% Marcaine (bupivacaine) was administered preoperatively. No intracameral or intravitreal medications were used. At the end of the case, dexamethasone and cefazolin were applied to the ocular surface.

At presentation, his vision was 20/100 and intraocular pressure (IOP) was 43 mmHg. There was no hypopyon, hyphema, significant corneal edema, or cellular reaction. The dilated fundus examination was unremarkable. Fibrinoid syndrome was suspected. He was started on topical prednisolone every 2–3 hours, brimonidine three times per day, timolol-dorzolamide two times per day, and orally administered acetazolamide. Within 2 weeks, the cords disappeared completely (Fig. 1b), vision improved to 20/30, and the IOP normalized off all medications.

Discussion
Fibrinoid syndrome was originally described in patients with PDR who underwent procedures such as pars plana vitrectomy (PPV), scleral buckling, and lensectomy [1]. The fibrin developed on the retinal surface or behind the iris 2–14 days after surgery and eventually progressed into a vitreous fibrous mass that caused tractional retinal detachment, iris neovascularization, and neovascular glaucoma. Despite oral and topical steroids, 9/15 (60%) patients progressed to no light perception vision. Patients with preoperative retinal detachment and those requiring multiple surgical procedures were significantly more likely to develop this syndrome.

Additional studies limited to the posterior segment described a “fibrinoid”, “web-like”, or “cobweb-like” response as thick vitreous cords that are responsive to steroids and resolve without sequelae [11–13].

A vitreous “web-like inflammatory response” was also noted in a patient with diabetic retinopathy who underwent PPV, membrane peel, and bevacizumab injection for an epiretinal membrane [12]. The authors postulated that this might have been a toxic anterior segment syndrome (TASS)-like or non-infectious endophthalmitis-like reaction to bevacizumab.

Thanos and coworkers described a patient in his 50s with diabetes who underwent uneventful PPV for non-clearing vitreous hemorrhage (NCVH) in the right eye and then developed “cobweb-like tan strands” and elevated IOP after PPV with endolaser for NCVH in the left eye [13]. Similar to our patient, the strands were responsive to frequent topical steroid drops and the elevated IOP was successfully managed with IOP-lowering medications. The cause of IOP elevation in both of these cases is probably the exuberant inflammatory response of fibrinoid syndrome; however, especially for anterior segment surgery, other etiologies such as insufficient viscoelastic removal should be considered as well.

Fig. 1

A Thick, rope-like fibrin cords in the anterior chamber 1 day after uncomplicated phacoemulsification with in-the-bag intraocular lens implantation. B The cords resolved 2 weeks after topical steroid administration.
Luo et al. reported on seven patients with PDR who developed a “transvitreal fibrinoid response” 1 day after PPV for diabetic sequelae [11]. Mean time to band resolution while on topical steroid therapy was 8.75 days, and correlated with vitreous band density.

In contrast to the thick, rope-like cords characteristic of the posterior segment, anterior segment “fibrinoid”, “fibrin”, or “fibrinous” reaction designates a more common finding that has a spectrum ranging from a few thin strands to a thick pupillary plaque [4, 5, 14].

Walinder and colleagues noted a “fibrinoid reaction” in 11–17% of patients undergoing ECCE with IOL placement [4]. It occurred 1–6 days after surgery, lasted up to 3 weeks, and morphologically ranged from a few strands to a dense pupillary membrane. There was no hypopyon, keratic precipitates, or vitreous reaction. Few patients developed posterior synechiae. The authors identified a significant association between fibrinoid reaction, pseudoxfolliation syndrome, and capsular glaucoma.

Baltatzis and coworkers determined the incidence of “fibrin reaction” in patients with diabetes without retinopathy (n = 102), primary open angle glaucoma with prior surgery (n = 78), and pseudoxfolliation without glaucoma (n = 43) as 13.7%, 44.8%, and 27.9%, respectively [5]. Similarly to Walinder et al. [4], the fibrin appeared between 3 and 12 days after surgery, was usually located in the pupillary area, resolved after a few weeks, and responded well to steroid therapy.

Jabbur described a patient with chronic leukemia and thrombocytopenia on aminocaproic acid who developed an anterior chamber “fibrinoid reaction” 1 day after phacoemulsification with IOL implantation [14]. There was no hypopyon, hyphema, or cellular reaction. Fibrin accumulation was attributed to the effects of aminocaproic acid on the blood–aqueous barrier (BAB). By a similar mechanism, mannitol has been shown to increase anterior chamber fibrinoid syndrome as opposed to the more typical anterior chamber fibrin reaction.

A previously published case of “fibrinous reaction” in a patient on aminocaproic acid [14] as well as reports of anterior chamber flare after mannitol administration [15] motivated us to closely examine the possibility of a pharmacologic cause for the clinical presentation in our patient. We identified ibrutinib as the most likely medication responsible as it has been shown to cross the BBB and induce anterior chamber changes [7, 8]. In the RONATE multicenter phase 3 study of ~400 patients with relapsed or refractory CLL or small lymphocytic lymphoma on ibrutinib versus ofatumumab (anti-CD20 antibody), 10% of patients on ibrutinib developed blurred vision and 3% developed cataracts [10]. The authors of the study warned that “longer exposure may be associated with an increased risk” of such adverse effects. In addition, Neffeendorf and colleagues reported “peculiar lens opacities” in an 80-year-old patient on ibrutinib for 6 months and suggested “precautionary baseline and repeated visual-acuity testing” in these patients [9]. Based on the above, it is reasonable to assume that, in addition to crossing the BBB, ibrutinib is able to cross the BAB and the blood–retina barrier.

In addition to inducing anterior chamber changes and the visual effects described above, we propose that ibrutinib’s pharmacologic mechanism of action may have contributed to the formation of thick fibrin cords in our patient. Platelet dysfunction is a well-documented side effect of ibrutinib [16]. Platelets are major producers of plasminogen activator inhibitor-1, which is an anti-fibrinolytic protein [17]. Fibrinolysis is an important component of fibrin resolution, and intracameral fibrinolytic agents such as tissue plasminogen activator (TPA) have been used to manage exuberant fibrin reaction in the anterior chamber [18]. Therefore, it is possible that ibrutinib-associated platelet dysfunction could lead to fibrinolysis inhibition ultimately resulting in our patient’s presentation. Interestingly, TPA is produced and localized to the uveal microvasculature, corneal endothelium, and trabecular meshwork [19]. Thus, ibrutinib could have contributed to our patient’s presentation through a direct intraocular effect via TPA dysregulation and fibrinolysis inhibition.

Finally, although ibrutinib has a strong safety profile and is generally well tolerated, a few patients developed neutrophilic panniculitis, which is an inflammatory infiltration of the subcutaneous adipose tissue [20]. An exuberant adaptive immune response against a novel hapten epitope (“drug-induced immune modulation”)
was proposed to explain the pathogenesis of this rare finding. The majority of patients were successfully treated with low-dose systemic corticosteroids. It is intriguing to think that this may represent an idiosyncratic proinflammatory reaction, and if a similar mechanism could have contributed to the findings in our patient.

**Conclusions**

The precise etiology of fibrinoid syndrome, especially of the anterior segment, remains unknown; however, it can be safely assumed that it is multifactorial. We present a case of anterior segment fibrinoid syndrome in a patient on ibrutinib for B-cell CLL after uncomplicated cataract extraction, and propose several mechanisms by which this medication could have caused this unusual clinical entity.

It is important to recognize fibrinoid syndrome in order to differentiate it from TASS and endophthalmitis, and to initiate appropriate treatment. The presentation is characterized by lack of pain, exuberant postoperative swelling/redness, significant corneal edema, or anterior chamber/vitreous reaction. Prompt initiation of anti-inflammatory therapy and close follow-up is paramount as the fibrin bands are exquisitely sensitive to topical steroids and resolve within a few weeks without permanent sequelae.

**Abbreviations**

BAB: Blood–aqueous barrier; BBB: Blood–brain barrier; CLL: Chronic lymphocytic leukemia; ECCE: Extracapsular cataract extraction; IOL: Intraocular lens; IOP: Intraocular pressure; NCVH: Non-clearing vitreous hemorrhage; PDR: Proliferative diabetic retinopathy; PPV: Pars plana vitrectomy; TASS: Toxic anterior segment syndrome; TPA: Tissue plasminogen activator

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Our manuscript is a case report. All collected patient data are available for review upon request.

**Authors’ contributions**
All authors participated in the clinical care of the patient. AMK and CKH performed data collection, literature search, and initial manuscript preparation. All authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**
This study conforms to the Health Insurance Portability and Accountability Act (HIPAA) and adheres to the Declaration of Helsinki and all applicable state and federal laws. Approval was not required as this is a case report of one patient.

**Consent for publication**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**
The authors declare that they have no competing interests.

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