

Ophthalmology

ROUNDS

As presented in the Grand Rounds and other Conferences of the Department of Ophthalmology from Massachusetts Eye and Ear Infirmary

Management of Exfoliation Syndrome

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While examining the anterior segment of a patient with slit lamp biomicroscopy, dandruff-like material is detected at the pupillary margin (Figure 1). This seemingly innocuous finding is a sign of a syndrome with many synonyms, but the term “exfoliation syndrome (ES)” is preferred. ES is a common age-related condition associated with significant ocular morbidity. Eyes with ES develop cataracts earlier¹ and have a higher risk of developing ocular hypertension and glaucoma² than eyes without ES. While phacoemulsification cataract extraction can be performed safely in eyes with ES, a higher rate of vitreous loss may occur because of zonular dialysis.³ Among patients with open-angle glaucoma (OAG), the presence of exfoliation material (EM) in the anterior segment is associated with a 2-fold increased risk of disease progression compared to the absence of this material.⁴ The following case illustrates some of the challenges faced in managing patients with ES.

Case presentation:

An 80-year-old Caucasian female of European origin presents with a chief complaint of having “trouble driving at night.” The patient was diagnosed with glaucoma 5 years previously and is unsure of her highest intraocular pressure (IOP). There was a history of follicular conjunctivitis with brimonidine use and periocular dermatitis with application of dorzolamide. Argon laser trabeculoplasty has been performed 360° in the right eye (no laser trabeculoplasty was performed OS). Her medical history is remarkable for hypertension, hypercholesterolemia, and peptic ulcer disease. The patient’s medications include verapamil, mevacor, ranitidine, and timolol 0.5% bid OU. There was no family history of glaucoma.

On examination at the Massachusetts Eye and Ear Infirmary (MEEI), her best-corrected visual acuity is 20/30 OD and 20/50 OS. The pupils are 4 mm OU and show normal reactions to light. Slit lamp examination is remarkable for white fibrillar deposits on the lens and iris in both eyes. There is 1+ nuclear sclerosis OD and 2+ nuclear sclerosis OS. Goldmann applanation tensions are 19 mm Hg and 26 mm Hg in the right and left eye, respectively. Pachymetry measurements reveal central corneal thicknesses of 545 microns OU. Gonioscopy reveals that the angles are open to the ciliary body band OU, with 1+ pigmentation of the trabecular meshwork OD and 2+ pigmentation of the trabecular meshwork OS. After dilation, peripheral and paracentral deposits of EM are evident on the lens surface of the left eye (Figure 2). Funduscopy reveals a cup-disc ratio of 0.75 OD and 0.50 OS. The peripheral retinal exam is unremarkable OU. Automated static perimetry, which is performed reliably in both eyes, reveals superior and inferior arcuate defects in the right eye and a shallow superior nasal step in the left eye (Figure 3).

The patient has a visually significant cataract in the left eye and is eager to have it removed. She had decided to seek a second opinion after her original ophthalmologist recommended that she have a combined procedure, ie, a cataract extraction combined with a trabeculectomy. She has a strong preference to avoid the additional filtration surgical procedure, if possible. How would you advise this patient?

Overview of exfoliation syndrome:

ES is a systemic disorder with predominately ocular manifestations. Clinically, ES is characterized by the deposition of grayish-white fibrillar material in a distinct pattern throughout the ocular anterior segment (see below for more details). Typically, ES is markedly asymmetric and often has a unilateral presentation. EM is made by cells in the lens, iris, and ciliary body, and is deposited on the corneal endothelium, trabecular meshwork, iris surface, lens, the zonule, and the ciliary body. Ultrastructural evaluations indicate EM can also be found in the conjunctiva, the orbit, and the walls of short posterior ciliary arteries. The extraocular distribution of EM includes skin, liver, heart, lung, and gallbladder, although these observations are limited to a small number of autopsy cases.^{5,6} While the ocular burden of ES is considerable, the clinical



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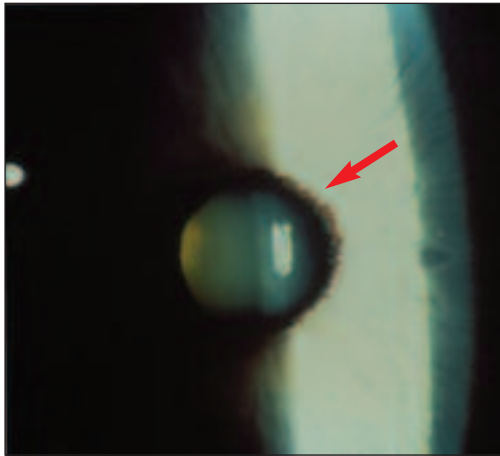
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Figure 1: Slit lamp photograph of a patient with ES showing fibrillar material at the pupillary margin (arrow)



consequences of extraocular EM deposition are thought to be minimal, although one group recently found more sensorineural hearing loss in patients with ES.⁷ More study is needed to determine if there are other extraocular manifestations of ES.

ES produces a myriad of clinical findings (Table 1). Careful slit lamp examination may reveal EM on the corneal endothelium (Figure 4) and, in the undilated state, fibrillar deposits may be noted at the pupillary margin, as well as pigment granules and EM on the anterior iris surface. Dilation of the pupils, which is often impaired in patients with ES, reveals fibrillar deposits on the lens capsular surface – this is how the diagnosis of ES is usually established. Early on, EM gives the lens capsular surface a ground-glass appearance; one may also see areas where the lens capsule seems transparent, presumably as a result of the sweeping motion of the iris across the lens (Figure 5a). A ring of EM may be present on the lens surface at the pupillary margin, but controversy exists as to whether there is actually a central disc of EM on the lens surface that corresponds to the pupillary aperture. Transillumination of the eye, which is

Figure 2: Slit lamp photograph of our patient after dilation showing peripheral and paracentral lenticular deposition of exfoliation material

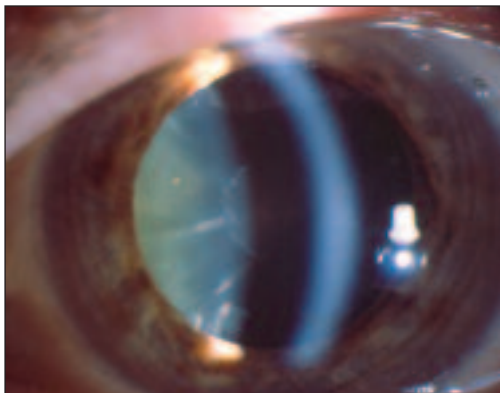


Figure 3: Standard automated perimetry of the central 24° of our patient performed with the Humphrey Visual Field Analyzer using the SITA-FAST algorithm. The test was tagged with a reliability warning the the right eye because of 23% fixation losses. There are superior and inferior arcuate defects in the right eye (shown on the left) and a superior nasal step in the left eye.



illustrated in Figure 5b, suggests a central disc of exfoliation may be absent in this particular patient.

As ES progresses, EM can coalesce into a sheet, which can give the impression that the capsule has split or delaminated (Figure 5c). This type of presentation may be confused with another condition where there is a schisis of the lens capsule that is classically caused by intense thermal exposure (such as can occur during glass-blowing). Traditionally, patients with lens capsular schisis were labeled as having “true” ES, while those with typical EM deposits throughout the anterior segment were described as having pseudoexfoliation (PXF) syndrome. In patients with “true” ES, the intraocular basement membranes split without producing exfoliative debris. In patients with PXF syndrome, there is actual exfoliation from the lens surface. Thus, the term “pseudo” is not an accurate description of the pathology. This inconsistency argues in favor of abandoning the term “pseudo” ES in favor of ES.

In patients with ES, gonioscopy (Figure 6) usually reveals an irregular pigmentation of the trabecular meshwork and Schwalbe's line. (N.B. A pigmented Schwalbe's line is often referred to as a Sampaolesi line). Pigmentation of Schwalbe's line, however, is not pathognomonic of ES. If the pupil is dilated or an iridectomy is present, gonioscopy may reveal that EM coats the zonular fibers or is deposited on the ciliary processes.

Composition of exfoliation material

In 1979, Ralph Eagle and colleagues hypothesized that ES resulted from aberrant production of basement membrane materials.⁸ More recent work, applying a proteomic approach to lens capsular tissue, suggests that the aberrant production of EM is related to complex processes that involve biochemical imbalance of enzymes involved in basement membrane turnover, complement activation, oxidative stress, ischemia, and inflammation.⁹ It is difficult to conceive of a unifying theory that explains the multifactorial pathophysiology in ES and currently the exact trigger that causes this excess fibrillar material to accumulate in the eye and elsewhere is unknown.

The pronounced deposition of EM in the eye may possibly relate to its unique embryologic development. Normally, basement membranes serve as an interface between surface lining cells and underlying stromal tis-

Table 1: The spectrum of clinical findings associated with exfoliation syndrome

Cornea	<ul style="list-style-type: none"> Fibrillar and pigment deposits Corneal decompensation, especially late after cataract extraction
Iris	<ul style="list-style-type: none"> Peripupillary iris atrophy* Intrastromal iris hemorrhage without rubeosis Poor pupil dilation Fibrillar and pigment deposits
Anterior chamber	<ul style="list-style-type: none"> Suspended exfoliation material and pigment especially after dilation
Lens	<ul style="list-style-type: none"> Fibrillar and pigment deposits Cataract Phacodonesis Late spontaneous subluxation of the lens (rare) Late spontaneous subluxation of the intraocular lens Fibrillar deposition on the intraocular lens (uncommon)
Angle	<ul style="list-style-type: none"> Irregular pigmentation of the trabecular meshwork and Schwalbe's line Fibrillar deposition on the trabecular meshwork, zonular fibers and ciliary body (if visible)
Applanation tonometry	<ul style="list-style-type: none"> Commonly higher IOP in the eye with exfoliation syndrome
Posterior segment	<ul style="list-style-type: none"> Pathologic optic nerve cupping Propensity to retinal venous occlusive disease

*This is not pathognomic of exfoliation syndrome

sue. Perhaps, in the anterior segment of the eye, where basement membranes face fluid-filled cavities, fibrillar material accumulates unencumbered by mechanical barriers normally created by stromal tissue. Table 2 lists the components of EM as determined from immunohistochemical and proteomic studies; many consist of a heterogeneous collection of macromolecules that are normally present in basement membranes. The ultimate elucidation of the chain of events contributing to ES may provide insight into ways to control the condition and hopefully reduce some of its ocular consequences.

Epidemiology of exfoliation syndrome

Patients presenting with ES are typically middle-aged (older than 50 years), although there are sporadic

Figure 4: Slit lamp photograph demonstrating exfoliation material deposited on the corneal endothelium (arrowhead).

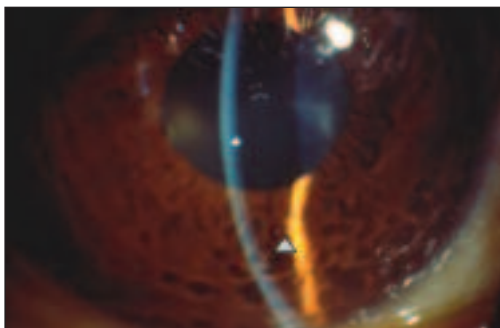
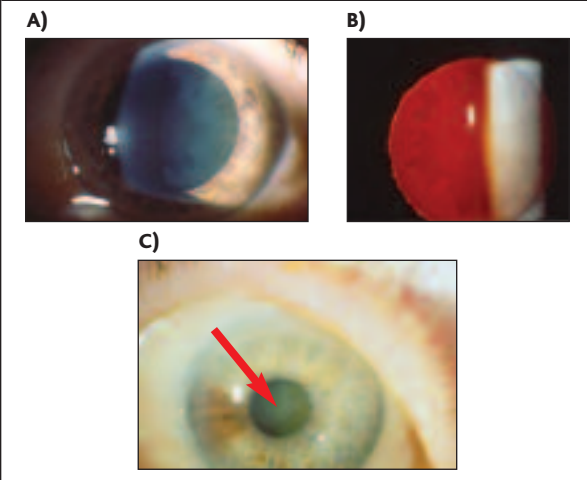


Figure 5: A) Dilated slit lamp photograph of a patient with ES showing the ground glass appearance to the peripheral lens capsule. There are some areas where the peripheral lens capsule is polished clean, presumably by the sweeping action of the iris. There is a hint of a central disc of exfoliation material. B) Trans-illumination of another patient with exfoliation syndrome shows peripheral deposition and a paracentral ring of exfoliation material, but no evidence of a central disc of fibrillar material. C) A patient with exfoliation material (arrow) that has coalesced into a sheet emanating from the central lens surface.



reports of the condition appearing during the teenage years. Unlike pigment dispersion syndrome, which has a male predominance, there appears to be no gender predilection for ES. Studies suggesting a male predominance in ES may be confounded by the fact that men spend more time outdoors and, thus, have higher solar exposures since the latter has been implicated in the pathogenesis of the disease.¹⁰

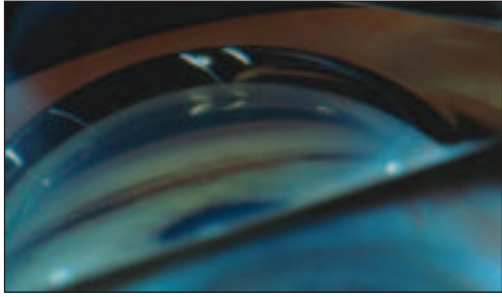
The prevalence and incidence of ES increases dramatically with age. In Finland, the prevalence of ES is 10% among those aged 60-69 years, but rises to 33% among those aged 80-89 years.¹¹ ES is virtually nonexistent among the Inuit people of Greenland¹⁰ and is uncommon among East Asians.¹² All other racial groups appear to be predisposed to develop ES, although there are highly varying prevalence rates among different ethnic groups.

Collectively, these observations suggest that a combination of genetic and environmental factors play a role in the development of ES; however, no specific environmental risk factors or genetic markers have been clearly identified and there is no consensus on the mode of inheritance. One study reported a high concordance rate among identical twins in Iceland, while an epigenetic study (that examined alteration in genetic markers in the ocular tissue of ES patients) found an alteration in markers on chromosome 7.¹³ Recent gene association studies have failed to demonstrate a relationship between an attractive candidate genetic marker – a polymorphism in the methylenetetrahydrofolate reductase gene (chr1p36.3) – and ES. This genetic variant was of interest because it produces hyperhomocysteinemia, which is a biomarker finding that some investigators have associated with ES.¹⁴

Mechanism of glaucoma in the exfoliation syndrome

When patients with ES develop glaucoma, the term “exfoliation glaucoma (EG)” is used. These patients have

Figure 6: Goniophotograph of a patient with ES showing irregular pigmentation of the trabecular meshwork and Schwalbe's line (the latter is referred to as a Sampaolesi line).



higher diurnal fluctuations in IOP than patients with primary open-angle glaucoma.¹⁵ In EG, dynamic irido-lenticular contact contributes to the release and redistribution of EM and pigment throughout the anterior segment of the eye, including within the trabecular meshwork. The accumulation of EM and pigment in the trabecular meshwork probably compromises outflow facility and contributes to elevated IOPs.

Management of glaucoma in ES

Ideally, the treatment of EG should involve halting the accumulation of EM and preventing the dispersion of pigment and fibrillar material throughout the anterior segment. Disassembly or evacuation of EM from the eye would theoretically also have therapeutic value. Since the cause of accumulating EM in the eye is unknown, it is not possible to institute a strategy by which accumulation of EM is halted. EM is extremely insoluble⁹ and it is not possible to safely dissolve it. Aspiration of EM from the eye has been tried, but is only temporarily successful.¹⁶ Specifically, when performed as a primary procedure in eyes with EG, trabecular aspiration of EM and pigment achieved a 20% IOP reduction on the first postoperative day in >80% of eyes. Only 23% of eyes enjoyed the same IOP reduction at 6 months. Some ophthalmologists have advocated early lens extraction as a means to reduce the release of EM and pigment, yet accumulation of EM can still occur in pseudophakic eyes. Some clinicians have suggested the use of pilocarpine to reduce iris movement, thereby reducing dynamic irido-lenticular contact and minimizing liberation of EM and pigment. However, neither maneuver has a basis in evidence-based medicine.

Without specific insights into the cause of ES, this disease by default is managed like other forms of glaucoma. Initial evaluation should always include careful gonioscopy to ensure the angle is open. In the setting of an open angle, EG can be managed like primary open-angle glaucoma. Similarly, if the angle is closed, consideration should be given to laser iridotomy. There are no glaucoma medicines that are contraindicated in EG. When medical therapy does not adequately lower IOP, laser trabeculoplasty has proven to be a useful next

Table 2: Molecular components of exfoliation material*

- Fibrillin-1
- Laminin
- Entactin/Nidogen
- Ibronectin
- Vitronectin
- Elastin
- Serum amyloid P
- Heparin sulfate proteoglycan
- Chondroitin sulfate proteoglycan
- Transforming growth factor beta 1
- Clusterin
- Tissue inhibitor of metalloprotease-3
- Fibulin-2
- Desmocollin-2
- Syndecan-3
- Versican
- Membrane metalloprotease of the ADAM family (a disintegrin and metalloprotease)
- The initiation component of the classic complement activation pathway C1q

* Modified from reference 9.

step, as long as care is taken to judiciously control the energy level that is applied to the trabecular meshwork, which is typically heavily pigmented. For argon laser trabeculoplasty, it is reasonable to start with an energy level of 500 milliwatts and carefully titrate the energy to achieve blanching of the trabecular meshwork upon laser application. For selective laser trabeculoplasty, if initial application of 0.6 to 0.8 millijoules results in projective bubble formation, the energy should be decreased.

Management of cataract extraction in ES

During surgery, it is important to viscodilate the pupil with an ophthalmic viscosurgical device. A dispersive or viscoadaptive agent is a reasonable choice to achieve simultaneous pupil expansion and corneal endothelial protection. Phacoemulsification can be performed through a 6.5 mm pupil, but any mechanical procedures to achieve sustained pupillary dilation should be taken. For pupils smaller than 6 mm, consider mechanical iris stretching or the use of iris hooks to achieve dilation; otherwise, progressive miosis during the procedure may make nuclear disassembly challenging.

The surgeon should note the response of the capsule during the initiation of continuous tear capsulotomy. Initial wrinkling suggests considerable zonular dialysis and, at that point, the use of capsular tension rings to stabilize the capsular bag should be considered. It is probably not necessary to use endocapsular support systems in every ES case. After hydrodissection and hydrodelineation, the nucleus may still be difficult to rotate. However, patience and gentle tension on the central nuclear tissue usually suffices to achieve adequate mobility of the nucleus. Some surgeons advocate “chopping” to remove the nucleus, but the surgeon should choose whatever technique that he/she is most comfortable with to remove the nucleus. Whatever technique is employed, it is important to use sufficient energy to adequately emulsify the nucleus to minimize stress on the zonules. After removal of the nucleus and cleanup of

the cortex, meticulous irrigation/aspiration must be carried out to remove any retained viscoelastic agent to reduce the chance of a postoperative IOP spike.

Back to the clinical case

Our patient has a denser cataract in her left eye, but more significant glaucomatous damage in the better-seeing right eye. The IOP is not well controlled in either eye and, while cataract surgery is clearly indicated in the left eye, it is reasonable to temporarily defer it to gain better IOP control in both eyes. Using this approach, latanoprost 0.005% qhs OU is prescribed, and target IOPs of ≤ 16 mm Hg OD and ≤ 18 mm Hg OS are arbitrarily assigned. In follow-up, the IOP is close enough to the target IOP in both eyes (17 mm Hg OD and 18 mm Hg OS) and a decision is made to perform cataract surgery alone in the left eye.

Preoperative considerations

At this point, the patient is on maximally-tolerated glaucoma therapy. While the IOP OS improves from baseline, the current tension is not ideal. Preoperative visits reveal that she has significant trabecular meshwork dysfunction, indicating that an early postoperative IOP spike is probable after cataract extraction alone. Fortunately, there is minimal visual field loss in the left eye and the pupil dilates to 6.5 mm. Furthermore, there is neither phacodonesis, nor asymmetry in the nasal and temporal anterior chamber depth, which suggests that there is no zonulodialysis. The cause of inherent zonular weakness, a well-known phenomenon in ES, is unknown, but could relate to low-grade enzymatic degeneration of zonular proteins.

It is reasonable to honor the patient's request to remove the cataract without performing glaucoma filtration surgery because the amount of visual field loss in that eye is mild. During the informed consent process, it is important to make the patient aware that, in addition to cataract formation, the left eye has considerable compromise of the outflow system. Thus, oral carbonic anhydrase inhibitors may be needed to lower the IOP in the early postoperative period.

Postoperative course

Our patient underwent clear-cornea cataract extraction with implantation of a posterior chamber intraocular lens (IOL) directly into the capsular bag. Her intraoperative course was unremarkable.

On postoperative day #1, her visual acuity was 20/60 OS and IOP was 28 mm Hg. The patient was started on steroid, topical antibiotic, and timolol. One dose of diamox 250 mg was given orally in the office, but not used thereafter.

On postoperative day #2, her vision was 20/25 and IOP was 17 mm Hg. Fortunately, the IOP in the unoperated right eye declined to the 14-16 mm Hg range on timolol and latanoprost.

Nine months later, the patient developed a visually-significant cataract in the right eye. Preoperatively, the vision was 20/40- and the IOP was 16 mm Hg on timolol and latanoprost. For the right eye, it seemed reasonable to offer the patient combined

cataract extraction with trabeculectomy. This eye, which is *status post* 360° argon laser trabeculoplasty, had considerable visual field loss and required maximal tolerated medical therapy to control IOP. Other therapeutic approaches that would have been reasonable might have included combining cataract extraction with endoscopic cyclophotocoagulation or an ab interno trabeculotomy with the trabectome. Long-term results with these newer forms of combined surgery were (and are still) not available at the time that the treatment plan was being formulated.

The patient refused combined surgery of any kind. Since she did well with the more limited approach to the fellow eye and given that the right eye dilated well, cataract extraction alone was performed. In advance of surgery, the patient was counseled that cataract extraction alone could produce uncontrolled IOP that might require subsequent glaucoma surgery.

A clear-cornea cataract extraction with insertion of a posterior chamber IOL into the capsular bag was performed without complication. On postoperative day #1, her vision was 20/200, the IOP was 30 mm Hg, and there was considerable inflammation in the anterior chamber. The patient was started on topical steroid every 2 hours, vigamox qid, and timolol 0.5% bid. Latanoprost was purposefully avoided because the prostaglandin analogs are relatively ineffective when the blood aqueous barrier (BAB) is disrupted in the immediate post-operative period, as would be expected on the first day after cataract surgery. Acetazolamide 500 mg po and one drop of brimonidine was given in the office. (It is reasonable to give only a single dose of brimonidine given the prior history of follicular conjunctivitis with this agent, as this non vision-threatening side-effect will not recur unless repeated doses are administered).

The next day, the IOP was 19 mm Hg and, over the next month, the IOP ranged between 19 and 22 mm Hg. By 1-month postoperatively, the initial intense anterior chamber inflammatory response had completely resolved, but a posterior capsular opacity (PCO) had developed. At this point, latanoprost was re-introduced because there was no cell or flare in the anterior chamber. At 2 months, the vision was 20/40 and the IOP was 14 mm Hg.

Conclusions

This patient's case illustrates several important points. The first point regards the challenges of managing co-existent cataract and EG, which is not an uncommon scenario in ophthalmic practice. In our case, cataract extraction alone assisted in controlling the glaucoma. The IOP was barely controlled with maximally-tolerated medical therapy preoperatively. Cataract surgery alone in both eyes resulted in transient increased IOP in the early postoperative period; however, long-term IOP levels were slightly better than they had been when the patient was phakic. Nonetheless, no dramatic reduction of IOP was attained after cataract surgery, illustrating the importance of assessing a patient's IOP several times preoperatively, especially when

there is considerable pre-existing glaucomatous optic neuropathy.

This experience is consistent with the results from a recent study by Damji et al,¹⁷ in which an IOP reduction of 1.85 mm Hg from baseline was noted in 72 ES patients who underwent cataract extraction alone after 2 years of follow-up, compared to an IOP reduction of 0.62 mm Hg from baseline in 112 patients without ES. Certainly, if the IOP had escalated further in the visits prior to cataract extraction in our case, it might have been necessary to insist on combining cataract extraction with glaucoma filtration of some sort. This is because one cannot expect miraculous reductions in IOP after cataract extraction alone in an eye with ES and a severely compromised trabecular meshwork, especially if there is significant pre-existing visual field loss. Should this patient develop uncontrolled IOP in the future, selective laser trabeculoplasty remains a viable option to manage her glaucoma prior to considering filtration surgery. Since the conjunctiva has not been manipulated, she would also be a good candidate for trabeculectomy or implantation of a glaucoma drainage device.

A second point should be made regarding the response of ES eyes to cataract surgery. It is interesting that the eye with more glaucomatous damage had the slightly slower visual recovery, longer sustained increased IOP, and early postoperative PCO. The cause of this unstable BAB is unknown, but may be related to the accumulation of EM in the walls of iris blood vessels that contribute to the BAB.

Finally, in our case, foldable acrylic lens implants were inserted into the capsular bag in both eyes because the zonular ring was found to have been intact intraoperatively. It should be noted that late subluxation of in-the-bag intraocular lenses (IOLs) has been reported in ES, which is presumably related to ongoing degeneration of the zonule. Spontaneous dislocations of the pseudophakos is clearly not occurring in epidemic proportions, so a blanket recommendation for placing IOLs in the sulcus cannot be made. Furthermore, routinely placing the IOL in the sulcus, where it comes in contact with uveal tissue, could have its own consequences in an eye with ES, such as exacerbation of glaucoma or the development of cystoid macula edema.

Key clinical points:

- Careful preoperative planning is needed to anticipate the complications of cataract extraction in exfoliation syndrome.
- Cataract extraction alone can have a long-term stabilizing influence on exfoliation glaucoma, possibly by reducing iris-lens contact, but there are patients with co-existent cataract and exfoliation glaucoma that may still need cataract extraction combined with trabeculectomy.

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Disclosure Statement: Dr. Pasquale is on the Speakers Bureau for Alcon Labs and on the Advisory Panel to the Innovation Factory.

This publication is made possible by an educational grant from

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