A 60-year-old man presented with a 2-year history of recurrent adenoviral keratitis in his right eye (OD). His previous corrected visual acuity (VA) was 1.00 in both eyes (OU), with a hypermetropic refraction of +2.00 D OU. Ophthalmological examination was normal, except for nuclear sclerosis of the crystalline lens OU. He had no relevant general medical history.

The keratitis resolved in one month, with persistence of subepithelial infiltrates that responded to topical fluorometholone or dexamethasone therapy, but which reappeared after discontinuation of treatment. Administration of 0.05% cyclosporine A eye drops were ineffective in treating the infiltrates. During the recurrences, the corrected VA decreased by between 1 and 3 lines, and the patient perceived some visual distortion and halos when looking at point light sources. He is presently on treatment with FML® eye drops/24-12h with occasional periods of interruption of 7-14 days at the patient’s discretion.

Figure 1. Central infiltrates at the time of the visit. Intermittent treatment with fluorometholone eye drops.

Figure 2. Anterior corneal topography, tangential map: Slight central irregular astigmatism.
In the last 6 months, there has been a myopic shift of 2.00 D in the prescription in the OD, with the presence of a nuclear cataract. The patient’s current situation is as follows:

Visual function: OD: 0.80. With −0.50 sphere: 1.00; Left eye (OS): 0.40. With +2.00 sphere: 1.00.

Biomicroscopy: OD: Faint central subepithelial infiltrates. Nuclear cataract + (N1C0P0); OS: Nuclear sclerosis of crystalline lens.

Intraocular pressure: OD: 15 mmHg; OS: 15 mmHg.

Eye fundus: Normal findings OU.

Corneal OCT: OD: Central corneal infiltrates with slight irregularity of the epithelial-stromal interface. Mean depth of 110 microns. In the periods of peak response to the corticosteroid, the depth decreases to around 40 microns.

Corneal topography: OD: slight central irregular astigmatism; OS: slight regular astigmatism.

The patient is very uncomfortable in both his working environment, performing office work, and personal life. If cataract surgery is considered, he also wishes to assess the possibility of implanting a multifocal intraocular lens.

There are two problems to be resolved in the clinical case in question: the first is the recurrence of epithelial infiltrates causing oscillations in the patient’s visual performance; secondly, if cataract surgery is proposed as an option, this should include analysis of multifocal intraocular lens (IOL) implantation.

Before considering cataract surgery, we would first attempt to stabilise the infiltrates, since these are a critical factor when deciding whether or not to implant a multifocal IOL. Infiltrates often tend to disappear with age and fluorometholone or dexamethasone treatment, as has been reported in this case. After cessation of both treatments, any recurrence is usually treated with 0.05%-2% cyclosporine A to reduce the formation of infiltrates and associated symptoms, such as foreign body sensation or decreased visual performance. Up to this point, the treatment applied in the clinical case seems to be logical and appropriate, and therefore we would have proceeded in the same way.

Following the lack of success, the use of steroids such as FML® eye drops/24-12 h is an alternative only in conditions complicated by the appearance of infiltrates or pseudomembranes. However, we would have chosen another treatment, considering the known side effects of steroids, which furthermore do not guarantee that there will be no recurrence. One of the alternatives to steroids that we would consider at this point is 0.03% tacrolimus (FK506) twice daily, although it is important to take into account that this treatment is not free from side effects, and may cause severe dizziness in some patients.
If none of the above options worked and the recurrences continued, transepithelial phototherapeutic keratectomy (PTK) using low dose mitomycin C could be performed, once the infiltrates had been classified as chronic, with no possible pharmacological treatment. This technique has been shown to improve both visual symptoms² and the recurrence rate⁴. Having taken the decision to perform PTK, a new question arises related to the depth of the ablation. The mean depth of the infiltrates is around 110 microns, although following treatment, this decreases to 40 microns in the period in which there is peak response to the corticosteroid. This would suggest that a depth of around 60 microns might be sufficient to avoid generating an excessive hypermetropic defect. However, the appearance of recurrences has been reported in deeper layers where there is no opacity. These findings lead to the hypothesis that the virus can penetrate beyond the subepithelial zone in which the opacities usually appear, with the excessive use of corticosteroids being one of the possible causes of this deeper penetration⁵. Bearing this in mind, and in order to reduce the likelihood of the infiltrates recurring, we would carry out the ablation up to 110 microns, and expect that the refractive defect in the right eye (OD) would change from −0.50 D to a value close to the +2.00 D of the left eye (OS). Although it would be ideal to know the hypermetropic defect induced a priori by the PTK to reduce the anisometropia of both eyes, this is not simple, since it will depend in part on the laser fluence⁶.

Having performed the PTK in the OD, we would wait to see the corneal response regarding possible recurrence of the infiltrates. It is important to highlight that the progression of the nuclear cataract will gradually correct the patient’s hypermetropic refractive defect and, once we have decided to perform the cataract surgery, the refractive defect induced by the PTK will be taken into account for the IOL calculation.

If having performed the procedure described above we found a regular cornea with no infiltrates, this will be the time to assess whether implantation of a multifocal IOL is possible, taking into consideration the additional complexity of calculating the IOL in the OD, since this is a cornea that has undergone laser surgery. If we rely solely on corneal optical quality criteria, we tend to use corneal aberrometry (RMS < 0.3 microns) and central keratometry at 4 mm obtained with the Pentacam Holladay Report to determine whether the optical quality of the cornea is good enough to interact properly with a multifocal IOL. If not, we would choose a monofocal IOL.

REFERENCES


Joaquín Fernández, MD
Almería, Spain

In the case presented, there are three problems to resolve: 1) the presence of recurrent adenoviral infiltrates in the right eye; 2) the nuclear cataract in the same eye; and 3) the anisometropia generated by the nuclear cataract and hypermetropia of the contralateral eye.

1. Recurrent adenoviral infiltrates in the right eye
Recurrent or corticosteroid-dependent adenoviral infiltrates cause symptoms such as glare, decreased visual acuity, halos, foreign body sensation and hyperaemia, and can persist for several years. Moreover, in this case, it is advisable that this be resolved before surgical treatment of the cataract in the same eye. If the infiltrates reappear after topical corticosteroid treatment, and have not responded to topical cyclopentolate, we would begin topical treatment with 0.03% tacrolimus, combined with a preservative-free topical corticosteroid for the first three weeks, as tacrolimus takes several weeks to start working. The initial regimen would be topical dexamethasone 3 times a week for the first week, tapering the dose by one drop per week until discontinuation in the fourth week, together with topical 0.03% tacrolimus twice daily, which would be maintained long-term after discontinuing the corticosteroid. Recent studies have shown its efficacy in cases of adenoviral infiltrates that have not responded to topical cyclosporine¹. The aim of treatment would be to inactivate the infiltrate, which generally requires around 5-6 months of tacrolimus treatment; as a consequence of the infiltrates, fainter leukomas usually remain that, in general, take longer to disappear. In this case, and given how long these have been present (2 years), residual faint leukomas probably remain,
which according to the image, occupy the visual axis. If, as appears likely, the leukomas do not disappear following tacrolimus treatment, we could consider treating them with excimer laser, once the inflammatory process has been inactivated. Although the success rate of this procedure is good in our experience, we must bear in mind that it is not 100%, as reported in the literature\textsuperscript{2,3}, and as we have seen in some of our own cases. Excimer laser treatment of infiltrates reduces glare, and improves corneal transparency, visual acuity, and contrast sensitivity. However, infiltrates can reappear again in 9% of cases after discontinuing post-operative topical corticosteroid treatment, and glare does not completely disappear in all cases\textsuperscript{2}. It must also be taken into account that the treatment induces a hypermetropic change. In the case presented here, excimer laser treatment could be performed before the cataract surgery, but this would complicate the intraocular lens (IOL) calculation. If the treatment is performed after the cataract surgery, the hypermetropic change induced would have to be taken into account, so it would be advisable to propose a myopic objective in the lens calculation. However, the lens calculation would be simpler, and excimer laser treatment after surgery would allow any other astigmatic refractive defect to be treated, so the possibility of post-surgical emmetropia would be higher. Therefore, we believe that it would be best to perform it after the cataract surgery.

2 and 3. Cataract surgery and resolution of the anisometropia
The patient has anisometropia of 2.5 D generated by the myopic shift of the right eye due to the nuclear sclerosis (he was previously hypermetrop of +2.0 D, the same as the contralateral eye). Lens surgery in the right eye is necessary, given the presence of the cataract, and once performed, will require lens surgery in the left eye (hypermetrope of +2.0 D) to resolve the anisometropia. In short, the surgery must be bilateral. To that end, and since treatment of the infiltrates in the right eye with tacrolimus is likely to last for a few months, we would propose reversing the order of operations, to provide the patient with the quickest possible visual rehabilitation and resolution of the anisometropia (he finds work uncomfortable). If refractive lensectomy of the left eye is performed on commencing treatment of the right eye with tacrolimus and corticosteroids, the resulting anisometropia will be -0.5 D (actual myopic shift of the right eye). This will give us the necessary time to finish treating the infiltrates in the right eye with minimal discomfort for the patient. This is a 60-year-old patient, with nuclear sclerosis and +2.0 D of hypermetropia, so it is a good case (if the rest of the examination is normal) for refractive lensectomy of the left eye. If the other findings on examination permit (state of eye fundus, pachymetry that enables laser enhancement, intraocular pressure, tear function, etc.), and the patient is interested in spectacle independence for near vision, we think that the doubt about the advisability of implanting a multifocal lens in the right eye should not affect the choice of multifocal lens for the healthy left eye. Our experience of monocular implantation of multifocal lenses is good, if we explain to the patient the advantages and the differences that he will perceive. In this case in particular, we would then perform a refractive lensectomy with implantation of multifocal lens in the left eye, while simultaneously commencing tacrolimus treatment in the right eye.

Once the tacrolimus treatment had been completed and the infiltrates inactivated, the cataract surgery on the right eye would have to be considered. If the leukomas disappear after treatment (which seems unlikely given the time since onset), and there are no recurrences of the infiltrates, we would suggest cataract surgery with implantation of a multifocal lens, as in the left eye.

The more likely scenario however, is that the leukomas will persist; moreover, according to the images, these are located in the visual axis. Although sometimes, as appears to be the case here, there can be surprisingly good visual acuities, these leukomas can cause glare, decreased contrast sensitivity, etc., all of which are unsuitable conditions for multifocal lens implantation. It should also be taken into account that adenoviral conjunctivitis can leave dry eye as a consequence, a condition which is also unfavourable for multifocal lens implantation. However, excimer laser treatment enables infiltrates to be resolved without recurrence in a significant percentage of cases, especially if mitomycin C is used. In addition, multifocal lenses are available that slightly sacrifice near vision in order to conserve better contrast sensitivity and have a lower incidence of dysphotopic phenomena, such as so-called “extended range of vision” lenses; in some cases we have combined these with a bifocal multifocal lens from the same manufacturer in the contralateral eye. For example, in this case, we would implant a Tecnis\textsuperscript{*} ZLB bifocal lens with +3.25 addition in the healthy left eye and a Symfony lens (extended range of vision) in the right eye, in case the leukomas in the right eye are not fully resolved with excimer laser after the cataract surgery. To that end, we think that using this type of lens, and by planning excimer laser treatment for the residual leukomas following the cataract surgery on the right eye, we could then also propose a multifocal implant in the right eye. With respect to the choice of lens, it is also important to take into account that, since we are going to perform a myopic ablation that will induce an increase in the corneal spherical aberration, we should choose a lens that compensates it with negative spherical aberration (the Symfony lens has asphericity of -0.27).

As regards the manoeuvres and techniques recommended, for the IOL calculation, it would be advisable to take keratometric measurements once the infiltrates are inactive. When there are active infiltrates, the elevation of the lesions generates corneal irregularities that can lead to erroneous measurements. Once the infiltrates have been inactivated (with corticosteroids or tacrolimus), even if the leukomas persist, the epithelium tends to regularise the corneal surface, so the measurements will be more reliable.
In relation to treatment of the residual leukomas with excimer laser following the cataract surgery, it is important to ensure that the previous pachymetry permits the treatment; a new OCT should also be performed at the end of the tacrolimus treatment, and the depth of the leukomas evaluated. According to the case description, during the corticosteroid treatments, the depth reached 40 microns below the epithelium, which would correspond to a residual of between −1.0 D to −1.5 D, according to the optical zone and type of laser used. This analysis is important to suggest a target in the IOL calculation which can then allow us to perform PRK that removes all, or almost all, the area of the leukomas. If we calculate the lens with a plano refraction target as usual, treatment of the leukomas with PTK would induce a hypermetropic change of between +1.0 D and +1.5 D, with a poor final refractive result.

In order to perform the PRK, it is also important to program a sufficiently wide optical zone to remove the most peripheral leukomas, and pay attention to the irregularity in the epithelium-Bowman's layer interface. In the case shown, this appears minimal, and we think that the treatment can be approached conventionally with mechanical de-epithelialisation after application of 20% alcohol, followed by myopic ablation; however, we have found major irregularities in Bowman's layer, which are “filled or compensated” by epithelium and are not detected in the topography, after treating some cases of old infiltrates, following mechanical de-epithelialisation after application of 20% alcohol. If the irregularities are very large, it is better to cancel the procedure, allow re-epithelialisation and then perform transepithelial ablation to remove the epithelium, using it as a mask to treat the irregularities. In order to avoid a hypermetropic outcome in these cases, in our experience it is advisable to reduce the myopic ablation by one third. In any case, the use of 0.02% mitomycin C is recommended, which we apply for 12 seconds; in addition to preventing haze, this seems to reduce the likelihood of recurrence of the adenoviral infiltrates, which has been described following PRK and PTK.

In my experience, adenoviral keratitis is generally inactivated and the leukomas clearly decrease 1-2 years after the infection. However, in a case such as the one discussed here, in which recurrences persist two years later with an increase in the size of the infiltrates and decreased vision despite treatment, we must attempt an effective method to both improve the patient's vision and to reduce the recurrences.

In this case I would suggest ablation treatment with excimer laser, with de-epithelialisation followed by stromal ablation of approximately 70-80 microns, which is the thickness of the infiltrates after corticosteroid treatment.

Initially, I would suggest phototherapeutic keratectomy (PTK). However, in order to later plan multifocal lens implantation and not cause an excessively high refractive defect, and with a clear increase in the spherical aberration, I would also suggest myopic/hypermetropic ablation > 7.5 mm in diameter, taking into account that we will make the final refractive correction with the multifocal lens implant.

Excimer laser ablation has been shown to improve visual acuity, reduce halos and glare, and decrease recurrences in patients with leukomas secondary to adenoviral keratitis. After the ablation treatment, it should be combined with 0.002-0.01% mitomycin for 30-60 seconds.

Post-operative treatment will include fluorometholone in a tapered dose for 10-12 days, topical antibiotics for 7-10 days, and artificial tears for at least 6 months.

Three to six months following the ablation with excimer, and providing that the outcome is satisfactory with no recurrences, we could perform the cataract surgery, suggesting implantation of a multifocal lens. The surgery should be bilateral, but not simultaneous, in my opinion.

REFERENCES


Victoria de Rojas, MD, PhD
A Coruña, Spain

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We would consider a satisfactory outcome to be that in which there was a drastic reduction in the leukomas. We could implant a multifocal lens providing that the final corneal spherical aberration is not greater than 0.3 - 0.4 microns, analysing the central 4 mm of the cornea.

In my opinion, the lens to implant should be a low addition (2.75 dioptres in plano lens) bifocal lens, which having a probable power of > 25 dioptres given the previous refraction, would be sufficient to provide good visual acuity at 40 cm and acceptable depth of focus.

REFERENCES


Pedro Tañá, MD
Alicante, Spain

The problem to resolve here is a case of post-adenoviral keratitis recurrent infiltrates, with development of a nuclear cataract that is producing bothersome anisometropia. It is important to plan sequential treatment of both problems due to the existing interrelationship.

As regards the procedure to follow, in my opinion, the corneal problem should first be resolved, leaving the cataract surgery for a second procedure.

Subepithelial infiltrates are a major clinical problem following adenoviral keratitis. They can occur in up to 50% of cases and persist for years with a variable level of intensity. Visual symptoms are generally controlled with topical corticosteroid treatment, using dexamethasone as a shock treatment and fluorometholone or rimexolone as maintenance treatment for several months. During this period, the minimal effective dose to control the problem must be empirically sought, and in the medium term (3-12 months), gradually reduce the treatment. When steroids are ineffective, or when recurrence after tapering-discontinuing them becomes the norm, similar treatment may be attempted with topical 0.05%–2% cyclosporine A and/or topical 0.03% tacrolimus (suspension or ointment). If medical treatments fail, the viral particles and anterior stromal scars need to be physically removed using phototherapeutic keratotomy (PTK) treatment with excimer laser, combined with intraoperative topical application of 0.02% mitomycin C.

In this case, and due to the concurrence of the cataract that will soon require surgical correction, my inclination would be to act directly with excimer laser. I would administer 2-3 weeks of treatment with fluorometholone eye drops every 8 hours, to reduce the lesional infiltration, and I would program a combined profile: 1) 55-micron PTK, which I would apply transepithelially to somewhat regularise the anterior stromal surface; 2) 20-micron PTK for the first part of the stroma; and 3) myopic photorefractive keratoplasty (PRK) with a 7.00-mm optical zone of about 3.0 D, which in total would generate a central ablation of around 70 microns. Looking at the depth of the central infiltrates on the optical coherence tomography (OCT), this should be sufficient to remove the lesions. Following the ablation, I would apply 0.02% mitomycin C for 30 - 40 seconds. The reason for combining a myopic profile in central ablations of > 20 microns is that the resulting corneal optic is more regular than in PTK mode, with a low degree of spherical aberration if we use a latest generation laser. Induction of hypermetropia is greater, but it will be later compensated with the aphakic intraocular lens (IOL) implanted.

The refraction resulting from this treatment will be about 3.0 D - 4.0 D of hypermetropia, with a certain tendency towards the lower value, due to possible cataract progression in the following 6-8 months. During this time, the ametropia will have to be corrected with spectacles and/or contact lenses. The patient’s functional situation will then have to be evaluated, and a decision made as to whether he requires cataract surgery in the right eye (OD). If so, two important points must be taken into consideration:

- The optical quality of the cornea: If it is good, with a reasonably low level of high order optical aberrations and absence of central leukomas, a multifocal IOL could be considered, either refractive, diffractive or mixed. If it is not, I would prefer to implant a monofocal lens to minimize secondary visual symptoms.

- Approach to follow with the contralateral eye. The usual procedure is that we indicate consecutive lensectomy and IOL implantation. This will be easier for the patient to accept if the IOLs are multifocal in both eyes, for the optical benefit obtained. If the IOL in the OD is eventually monofocal, my preference would be to implant a monofocal lens in the left eye (OS), perhaps seeking micro-monovision as a refractive objective. Implantation of a multifocal lens in the OS, combined with the monofocal lens in the OD could be something to consider, following an extensive, clear discussion with the patient.

Finally, in relation to the surgical manoeuvres, an interesting option (if the configuration of the
surgical area allows) would be intraoperative control of the ablation depth using OCT. On reaching the programmed ablation depth, the patient leaves the operating room to monitor the efficacy of the treatment with corneal OCT. If persistence of residual lesions is observed, a greater level of laser ablation is performed.

The most important factor in the cataract surgery of the OD is to employ the correct method for calculating the IOL, bearing in mind the alteration in the anterior curvature/posterior curvature ratio that the surface ablation will have produced. A double K formula should be employed if using a formula that uses corneal information to estimate the position of the IOL. Another option is to use the Haigis-L formula, which empirically compensates the anterior keratometry. A third option is to use direct measurement of the posterior side (Scheimpflug or OCT) in software that uses this information properly, such as Okulix or Phacooptics.

REFERENCES


Luis H. González, MD
Vitoria-Gasteiz, Spain

This is a clinical case characterised fundamentally by the presence of adenoviral subepithelial infiltrates (SEI). Adenoviral keratitis is classified into various grades according to the time since onset, while the case presented corresponding to grade IV or V1. In grade IV, the epithelium that covers the SEIs does not stain with fluorescein and has a normal appearance, while in grade V, the epithelium is altered and has an appearance that has been described as "granular". In both cases, and despite the appearance of collagenous corneal scarring, the histopathological basis of SEI is a lymphocytic infiltrate in the deep epithelium and anterior stroma, produced by an inflammatory reaction of immune origin against viral antigens1. These chronic SEIs can be important, causing the visual disturbances presented by the patient here.

Furthermore, in this case, the patient also has a mild cataract in the same eye, perhaps related with the steroid treatment.

The problem to be resolved is clearly the corneal involvement, which is probably causing most of the patient’s symptoms. After this has been resolved, the degree of visual impairment caused by the cataract can be assessed, and then surgically corrected, if necessary. There is a second reason for proceeding in this manner: the problem of the accuracy of the biometric calculation of the power of the intraocular lens (IOL) to be implanted when the patient has a cornea with opacities and some degree of irregular astigmatism. Once the optical quality of the cornea has improved, the biometry will undoubtedly be much more accurate.

Since various anti-inflammatory treatments have already been tried in this case, with the SEIs nonetheless persisting two years after the initial episode, my advice would be to perform phototherapeutic keratectomy (PTK). Although there are few published studies on the efficacy of PTK in this context, the combination of non-aggressive PTK (as regards the amount of cornea ablated—less than 25 microns) and the application of intraoperative mitomycin C (MMC) has been reported to obtain good results in chronic SEIs2.

My approach therefore would be:

1) Transepithelial PTK with stromal ablation depth of 25 microns
2) Application of 0.02% MMC for 2 minutes
3) Usual post-operative treatment following surface ablation, i.e. FML 3 × day for 4 weeks, and topical antibiotic until re-epithelialization.
4) Assessment of the case 3 months after the PTK; if the cataract is visually relevant, the cornea has recovered normal transparency and keratometry is fine, I would proceed with cataract surgery. I would personally use a monofocal lens, since the contralateral eye has almost no cataract. Moreover, after long-standing SEIs, and following excimer ablation, corneas often have mild residual opacity and at the very least an alteration in the tear film, facts that may mean that the patient does not adapt to a multifocal lens. Nevertheless, if the patient agrees to bilateral surgery, and the right cornea had very good transparency after the PTK, implantation of a multifocal lens could be assessed as an option.

Treatment of corneal involvement within the context of adenoviral keratitis is controversial, and topical anti-inflammatory drugs are essentially the treatment of choice. In this respect, a controlled study reported that non-steroidal anti-inflammatory drugs (NSAIDs) are no more effective than lubricating eye drops1, while cyclosporine eye drops3 and steroids3 are effective, especially in the early stages. Unfortunately, as in the case presented, relapses are common, and the tendency for some cases to become chronic means that more aggressive treatments, such as PTK, must be applied.

Contrary to popular belief, the aim of PTK is not to remove all the stroma affected by the SEI, but only part of it2; as these have a major inflammatory component and are not strictly collagenous stromal scars, partial...
removal of the affected stroma is sufficient to resolve them, since there is a reduction in the antigen load that decreases the immune activity responsible for the SEIs.

In another clinical context, such as the complication known as “haze” that can occur following excimer surface ablation, the behaviour of the cornea is similar, i.e. the superficial opacities are not completely removed by ablation or debridement of the affected area; rather, it is the intraoperative application of the MMC that is responsible for the keratocyte apoptosis and subsequent inhibition of cellular mitosis, resulting in disappearance of the stromal opacities. Furthermore, the intraoperative application of 0.02% MMC on the cornea following laser surface ablation has been shown to be safe (no significant epithelial, endothelial or stromal toxicity) and very effective in preventing haze.

REFERENCES


Miguel A. Teus, MD, PhD
Madrid, Spain