False corneal ectasia in patients referred for corneal crosslinking, topography-guided photorefractive keratectomy, and intrastromal corneal rings

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ABSTRACT • RÉSUMÉ

Objective: To determine the misdiagnosis of ectasia in patients referred for corneal crosslinking and possible topography-guided photorefractive keratectomy (PRK) or intrastromal corneal rings.

Setting: Bochner Eye Institute, Toronto, Ontario, Canada.

Design: Retrospective data review.

Methods: Chart review of consecutive cases referred for corneal crosslinking to determine the number of cases of misdiagnosis of ectasia. Examination findings were reviewed consisting of best-corrected spectacle distance acuity, slit lamp examination, and computerized tomography.

Results: The study analyzed 1000 consecutive records of patients referred with a presumed diagnosis of keratoconus, pellucid marginal degeneration, and ectasia after laser vision correction that were examined between January 1, 2010 and November 1, 2016. There were 26 eyes without ectasia detected in 20 patients. The etiology of these misdiagnoses was epithelial basement membrane dystrophy (9 eyes), superficial punctate keratitis (7 eyes), amblyopia secondary to high astigmatism (3 eyes), amiodarone keratopathy (2 eyes), corneal warpage from rigid gas permeable lenses (2 eyes), corneal scars (1 eye), and measurement or alignment error with topography (2 eyes).

Conclusion: Analysis of data detected a misdiagnosis of ectasia in 20 patients (26 eyes), a finding of 2.0% (20 of 1000) of referred cases that did not satisfy the diagnostic criteria of corneal ectasia. These conditions are considered a contraindication to corneal crosslinking and there is usually no benefit to topography-guided PRK or intrastromal corneal rings. It is important that clinicians recognize the clinical findings of these conditions and differentiate from true keratoconus, pellucid marginal degeneration, or ectasia after laser vision correction.

Objectif: Évaluer le taux de diagnostic erroné d'ectasie cornéenne chez des patients adressés à l'Institut en vue d'une réticulation du collagène cornéen ou, éventuellement, d'une kératectomie photoréfractive guidée par topographie ou de l'implantation de segments d'anneau cornéen intrastromal.

Établissement: Bochner Eye Institute, Toronto, Ontario, Canada.

Nature: Revue de synthèse rétrospective des données.

Méthodes: Analyse des dossiers médicaux de cas consécutifs adressés en vue d'une réticulation du collagène cornéen afin de déterminer le nombre de cas de diagnostic erroné d'ectasie cornéenne. Les examens qui ont été passés en revue portaient sur la meilleure acuité visuelle corrigée de loin, l'examen à la lampe à fente et la tomographie assistée par ordinateur.

Résultats: L'étude portait sur 1000 dossiers consécutifs de patients adressés à l'Institut en raison d'un diagnostic présumé de kératocône, de dégénérescence pellucide marginale et d'ectasie après une correction de la vision au laser; les patients ont été examinés entre le 1er janvier 2010 et le 1er novembre 2016. On a recensé 26 yeux sans ectasie chez 20 patients. L'étiologie de ces diagnostics erronés était la dystrophie cornéenne de la membrane basale épithéliale (9 yeux), la kératite ponctuée superficielle (7 yeux), l'amblyopie secondaire à un astigmatisme prononcé (3 yeux), la kératopathie à l'amiodarone (2 yeux), la déformation de la cornée induite par les lentilles rigides à haute perméabilité au gaz (2 yeux), les cicatrices cornéennes (1 œil) et une erreur de mesure ou un défaut d'alignement lors de la topographie (2 yeux).

Conclusion: L'analyse des données a fait ressortir un diagnostic erroné d'ectasie chez 20 patients (26 yeux), c'est-à-dire que 2,0 % des cas (20 sur 1000) adressés à l'Institut ne répondaient pas aux critères diagnostiques d'ectasie cornéenne. Or, ces atteintes sont considérées comme une contre-indication à la réticulation du collagène cornéen, sans compter que la kératectomie photoréfractive guidée par topographie ou l'implantation de segments d'anneau cornéen intrastromal n'apportent habituellement aucun effet bénéfique. Les cliniciens ont donc intérêt à reconnaître les caractéristiques cliniques de ces atteintes et à les distinguer des cas véritables de kératocône, de dégénérescence pellucide marginale ou d'ectasie après une correction de la vision au laser.

Patients with keratoconus, pellucid marginal degeneration, and ectasia after laser vision correction (LASIK, photorefractive keratectomy [PRK], or small incision lenticule extraction [SMILE]) may benefit from corneal crosslinking (CXL)[1] to stiffen a cornea and prevent progressive ectasia. In contrast, eyes without ectasia do not typically benefit from CXL. It is not uncommon for clinicians to have difficulty in diagnosing an eye with a true ectatic disease.[2]

The diagnosis of an ectatic disease is commonly made with a slit lamp examination, determination of best-corrected spectacle acuity, refraction, and corneal topography and (or) tomography. In the early stages of an ectatic disease, slit lamp examination, acuity, and refraction may be normal. Advances in corneal imaging have provided valuable elevation data on both the anterior and posterior surfaces. In addition, pachymetry data can provide additional information to help diagnosis an ectatic disease.

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There are a wide variety of conditions that can be misdiagnosed with keratoconus, which include epithelial basement membrane dystrophy, superficial punctate keratitis, corneal scar, whorl-like keratopathy secondary to drug deposition, corneal warpage resulting from contact lens wear, amblyopia secondary to high astigmatism, and measurement error with topography.

This article is a retrospective review of patients referred for CXL and possible topography-guided (TG)-PRK or Intacs, with a presumed diagnosis of keratoconus, pellucid marginal degeneration, and ectasia after laser vision correction. We present our findings of the number and etiology of misdiagnosis of keratoconus and clinical points to differentiate these conditions from ectatic diseases.

Method

Patients were assessed for candidacy of CXL, topography-guided PRK, and intracorneal rings with a detailed history, ophthalmic examination, and corneal imaging. History included detailing possible eye rubbing, family history of keratoconus, and contact lens history. Examination included measurement of uncorrected visual acuity, corrected distance spectacle visual acuity, pinhole visual acuity, intraocular pressure, slit lamp examination, and dilated fundus examination. Scheimpflug technology was utilized using the Pentacam to evaluate anterior curvature, anterior elevation, back surface elevation, and pachymetry.

Differentiation of an ectatic cornea from a normal cornea was based on the Belin-Ambrosio Enhanced Ectasia Display (BAD).[3] The BAD display (available on the Pentacam; OCULUS GmbH, Wetzlar, Germany) utilizes both anterior and posterior elevation data and pachymetric data to screen for ectatic disease. It utilizes the elevation data against the commonly used best-fit-sphere taken from the central 8.0 mm zone and incorporates a new reference referred to as the enhanced reference surface. The BAD display has been shown to enhance the sensitivity and specificity of differentiating normal eyes from keratocous.[3,4]

Patients that showed anterior curvature changes suggestive of keratoconus but without posterior elevation changes had a more detailed slit lamp examination utilizing fluorescein dye and a cobalt blue light to look at corneal staining or an abnormal breakup of fluorescein suggestive of surface irregularities such as a superficial punctate keratopathy or epithelial basement membrane dystrophy.

Table 1—Twenty-six eyes were identified in 1000 patients referred for CXL, TG-PRK, and ICR

Pseudokeratoconus Conditions	Eyes (n)
Epithelial basement membrane dystrophy (EBMD)	9
Superficial punctate keratitis (SPK)	7
Amblyopia secondary to high astigmatism	3
Whorl-like keratopathy	2
Corneal warpage secondary to contact lenses	2
Corneal scars	1
Measurement error with topography	2

CXL, corneal crosslinking; TG-PRK, topography-guided photorefractive keratectomy; ICR, intracorneal rings.

Results

Between January 1, 2010 and November 1, 2016 there were 1000 patient screenings for CXL, topography-guided PRK, and intracorneal rings to identify keratoconus, pellucid marginal degeneration, and ectasia after LASIK or PRK. In 26 eyes (20 patients) there was no evidence of ectatic disease (Tables 1 and 2). The etiology of these cases was epithelial basement membrane dystrophy (9 eyes, 7 patients), superficial

Table 2—Findings in 20 patients, 26 eyes with pseudokeratoconus

Patient	Eyes	Age (years)	Sex	Diagnosis	Refraction	BCSVA	K Max (D)	Minimum Pachymetry
1	1	47	M	EBMD	−4.50 −1.75 × 77	20/25	47.1	570
	2	47	M	EBMD	−3.50 −3.50 × 25	20/40	47.5	586
2	3	37	F	EBMD	−2.00 −1.50 × 85	20/25	46.3	520
	4	37	F	EBMD	−1.25 −2.25 × 65	20/30	45.5	512
3	5	39	F	EBMD	+3.00 −2.75 × 65	20/30	45.8	565
4	6	22	F	EBMD	−7.50 −3.00 × 50	20/25	46.7	510
5	7	55	M	EBMD	−8.00 −4.00 × 182	20/50	52.2	550
6	8	27	M	EBMD	−6.50 −0.75 × 145	20/30	43.5	515
7	9	19	M	EBMD	−3.73 −1.00 × 82	20/25	46.3	501
8	10	44	F	SPK	−7.00 −2.00 × 148	20/30	48.3	515
	11	44	F	SPK	−5.25 −3.00 × 165	20/30	47.4	574
9	12	28	F	SPK	+3.00 −4.75 × 75	20/30	45.8	527
10	13	26	M	SPK	−6.50 −4.50 × 54	20/40	47.7	509
11	14	47	F	SPK	−3.00 −1.75 × 77	20/60	44.3	526
12	15	28	F	SPK	−7.00 −5.00 × 89	20/40	48.7	550
13	16	32	M	SPK	−5.50 −2.00 × 155	20/25	46.4	543
14	17	28	M	Amblyopia	+3.75 −4.50 × 65	20/40	48.8	535
	18	28	M	Amblyopia	+3.00 −4.25 × 78	20/30	47.5	564
15	19	36	F	Amblyopia	−6.50 −4.75 × 67	20/30	46.8	508
16	20	66	F	Amiodarone	+2.50 −1.75 × 45	20/30	46.8	560
	21	66	F	Amiodarone	+2.00 −2.00 × 175	20/25	45.7	506
17	22	28	F	Warpage	−7.00 −1.75 × 180	20/80	49.1	530
	23	28	F	Warpage	−5.20 −3.75 × 89	20/60	47.1	546
18	24	67	M	Corneal scar	−3.70 −1.80 × 003	20/30	46.5	567
19	25	32	M	Topographic error	−2.50 −1.00 × 085	20/20	44.2	540
20	26	27	F	Topographic error	+4.00 −1.75 × 175	20/20	43.0	532

BCSVA, best-corrected spectacle visual acuity; EBMD, epithelial basement membrane dystrophy; SPK, superficial punctate keratitis.

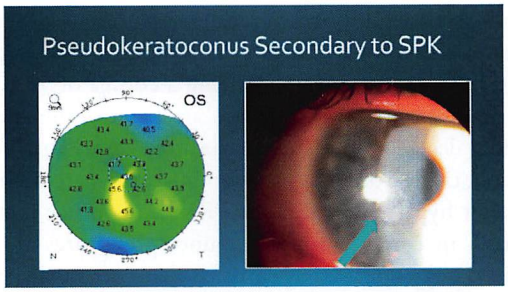

Fig. 1—SPK creating a pseudokeratoconus pattern on computerized topography. SPK, superficial punctate keratitis.

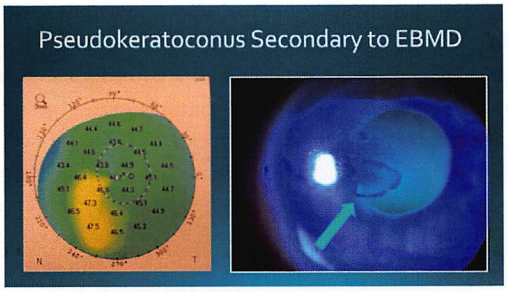

Fig. 2—EBMD can create a pseudokeratoconus pattern on computerized topography. EBMD, epithelial basement membrane dystrophy.

punctate keratitis (7 eyes, 6 patients), amblyopia secondary to high astigmatism (3 eyes, 2 patients), amiodarone keratopathy (2 eyes, 1 patient), corneal warpage from rigid gas permeable lenses (2 eyes, 1 patient), corneal scars (1 eye, 1 patient), and measurement error on topography (2 eyes, 2 patients). None of these patients had prior LASIK or PRK. Patients were counselled that they did not have an ectatic disease and that CXL, topography-guided PRK, or intracorneal rings were not required.

Case examples

1. A 52-year-old male was referred with a diagnosis of keratoconus for CXL and topography-guided PRK. Computerized topography showed inferior steepening suggestive of keratoconus (Fig. 1). Slit lamp examination showed mild trichiasis and superficial punctate keratitis (SPK). Elevation topography showed no evidence of posterior elevation. Corneal thickness maps showed no thinning in the area of steepening. The cilia were epilated and preservative-free artificial tears were used. The SPK resolved and the irregular curvature changes normalized on topography.
2. A 34-year-old female was referred with a diagnosis of keratoconus for possible CXL. The patient had reduced best-corrected spectacle acuity (BSCVA) of 20/30, and computerized topography showed prominent inferior steepening (Fig. 2). Slit lamp examination using fluorescein showed an abnormal breakup suggestive of epithelial basement membrane dystrophy (EBMD). A superficial keratectomy was recommended to enhance her vision.
3. A 55-year-old male was referred for CXL and topography-guided PRK in the management of his unilateral keratoconus. BSCVA was reduced to 20/50. Computerized topography showed evidence of temporal steepening to 53.0 D, suggestive of keratoconus (Fig. 3). Elevation tomography showed no posterior elevation. Pachymetry showed no thinning in the steepest area of curvature topography. Slit lamp examination with fluorescein dye and a cobalt blue light were unremarkable. This was suggestive of an atypical case of EBMD in which the slit lamp signs were not present. An epithelial debridement was performed. Five minutes after the procedure, topographic imaging was performed, which showed resolution of the prominent steepening. This confirmed that the corneal irregularity was in the epithelium and not the stroma. No further treatment was required.
4. A 66-year-old female was referred for an assessment of irregular astigmatism with a reduced BSCVA to 20/40. Computerized topography showed a curvature map with inferior steepening (Fig. 4). She was taking amiodarone, and slit lamp examination showed a whorl-like keratopathy to the inferior cornea. Elevation topography showed no evidence of posterior elevation. Pachymetry maps

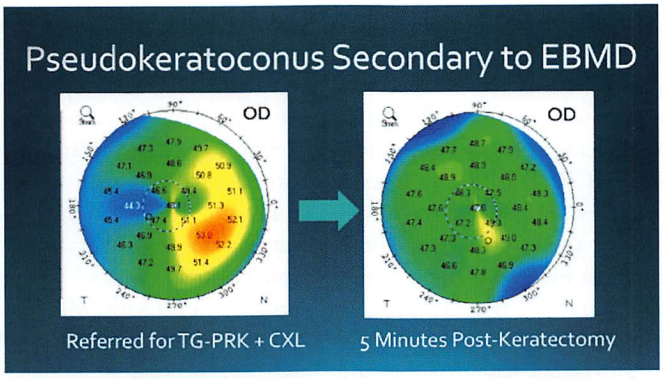

Fig. 3—Patient referred for TG-PRK and CXL that had findings suggestive of EBMD. Five minutes after a superficial keratectomy the corneal surface was normalized. TG-PRK, topography-guided photorefractive keratectomy; CXL, corneal crosslinking; EBMD, epithelial basement membrane dystrophy.

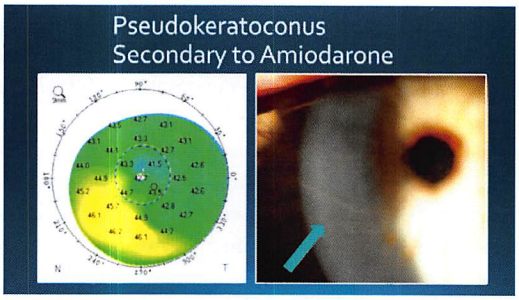

Fig. 4—Amiodarone keratopathy showed inferior steepening suggestive of keratoconus.

showed no significant thinning in the area of steepening. No treatment was recommended.

5. A 28-year-old female was referred for treatment of her keratoconus. She had been wearing rigid gas permeable lenses for 6 years. BSCVA was 20/80 and computerized tomography showed marked temporal steepening to 49.1 D (Fig. 5A). Minimum corneal thickness was 550 microns, and this was in the flattest area. There was no posterior elevation in the steep area. Tomography normalized after 7 weeks of discontinuing her contact lenses (Fig. 5B).
6. A 34-year-old male was referred for unilateral keratoconus. Best corrected spectacle visual acuity was 20/20 in both eyes. The tomography image that was taken at the referring doctors office showed inferior steepening in 1 eye with an inferior to superior difference of 6.6 D. Analysis of the tomography showed the pupil to be decentered inferiorly indicating a probable alignment error (Figure 6A). Repeat tomography with proper alignment was performed, which showed a normal anterior corneal tomography (Fig. 6B) and an inferior to superior difference of 0.3 diopters.

Discussion

A detailed patient screening for keratoconus, pellucid marginal degeneration, and ectasia is critical in order to make an accurate diagnosis and identify the best candidates for surgical intervention. The primary goal of CXL is to prevent progressive corneal ectasia. The role of topography-guided PRK and intracorneal rings is to reduce irregular astigmatism and hence improve best-corrected spectacle visual acuity. If the irregularity is caused by purely an epithelial problem or transient stromal changes, it is a contraindication to use CXL, TG-PRK, or ICR. TG-PRK induces a permanent change to the corneal curvature by removal of tissue. Intracorneal rings (ICR), with the insertion of 1 or 2 rings, can alter irregular astigmatism by a permanent structure in the cornea. If a patient were to have TG-PRK or ICR because of an epithelial disorder, and postoperatively the epithelium changes, the improvement would negate the effects of the procedure. In the case of TG-PRK or ICR, one could potentially induce irregular astigmatism and a reduction in best-corrected spectacle visual acuity.

CXL is an established procedure to prevent progressive ectasia by stiffening a cornea. The procedure has a reported long-term success rate in stabilizing a cornea of 98%.[1] The main indications today for CXL are keratoconus, pellucid marginal degeneration, and ectasia after LASIK or PRK. In addition, the use of CXL has been shown to decrease regression after hyperopic LASIK or PRK[5] and reduce microbial infection in corneal ulcers.[6] Adjunct procedures are available in many countries to enhance best-corrected spectacle acuity by the insertion of intracorneal rings or topography-guided PRK.

Epithelial basement membrane dystrophy is characterized by corneal epithelial changes that may appear like fingerprint lines, map-like changes, or microcysts.[7] These changes create surface irregularity and can be responsible for a pattern on anterior elevation or curvature topography that resembles keratoconus. Elevation topography of the posterior corneal surface would not show evidence of significant elevation. The steepest part of the cornea on curvature topography would not be correlated with thinnest spot with pachymetry. Slit lamp examination under cobalt light with fluorescein dye will aid the clinician in making the correct diagnosis of EBMD. An abnormal breakup of fluorescein is typically seen overlying the irregular corneal epithelium. If best-corrected visual acuity is reduced or quality of vision is affected then a keratectomy (i.e., debridement) can be performed. By removal of the irregular epithelium, a smoother epithelial surface can usually be created.

A focal corneal scar, secondary to an ulcer, inflammation, or trauma, may cause corneal flattening with a surrounding area of steepening that may resemble keratoconus on curvature topography. It is important to differentiate this corneal scar from that of keratoconus. Patients with keratoconus can often have associated corneal scars. Posterior topographic imaging will typically show posterior elevation. Although Scheimpflug devices may not give accurate corneal thickness measurements in the presence of a scar, the area of flattening will be the thinnest spot and not the area of steepening. In addition, keratoconus is usually a bilateral condition, and if the corneal scar is not secondary to keratoconus, the other eye will typically be normal. Although CXL is contraindicated in eyes with nonectatic diseases secondary to corneal scars, some patients may benefit from TG-PRK. The use of TG-PRK can reduce irregular astigmatism and potentially improve best-corrected spectacle acuity provided the scar tissue is not significantly deep, large, and overlying the pupil.

SPK can be secondary to a dry eye, blepharitis, trichiasis, corneal exposure such as lagophthalmos, chemical toxicity from topical medications or solutions used to rinse or disinfect contact lenses, or from mechanical trauma or hypoxia from contact lenses.[8–10] Computerized topography performed in eyes with SPK may show focal areas of steepening creating an irregular topographic pattern. Slit lamp examination with or without fluorescein dye will identify SPK. Elevation topography will show a normal pattern of posterior elevation. A corneal thickness map will not show any significant thinning in the area of prominent steepening. SPK is

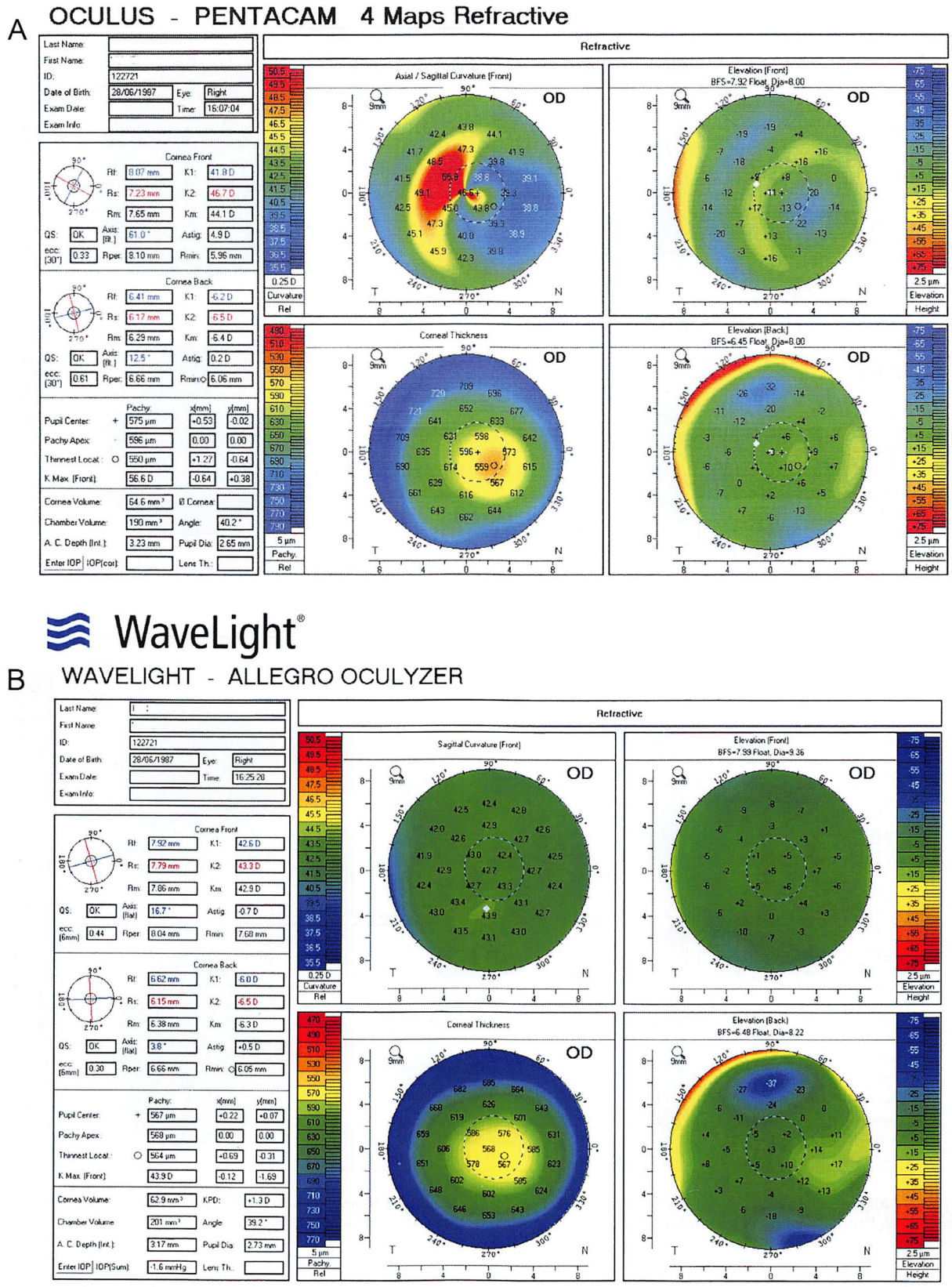

Fig. 5—A, Corneal warpage secondary to rigid gas permeable lenses. B, Resolution of corneal warpage 6 months after discontinuing contact lens wear.

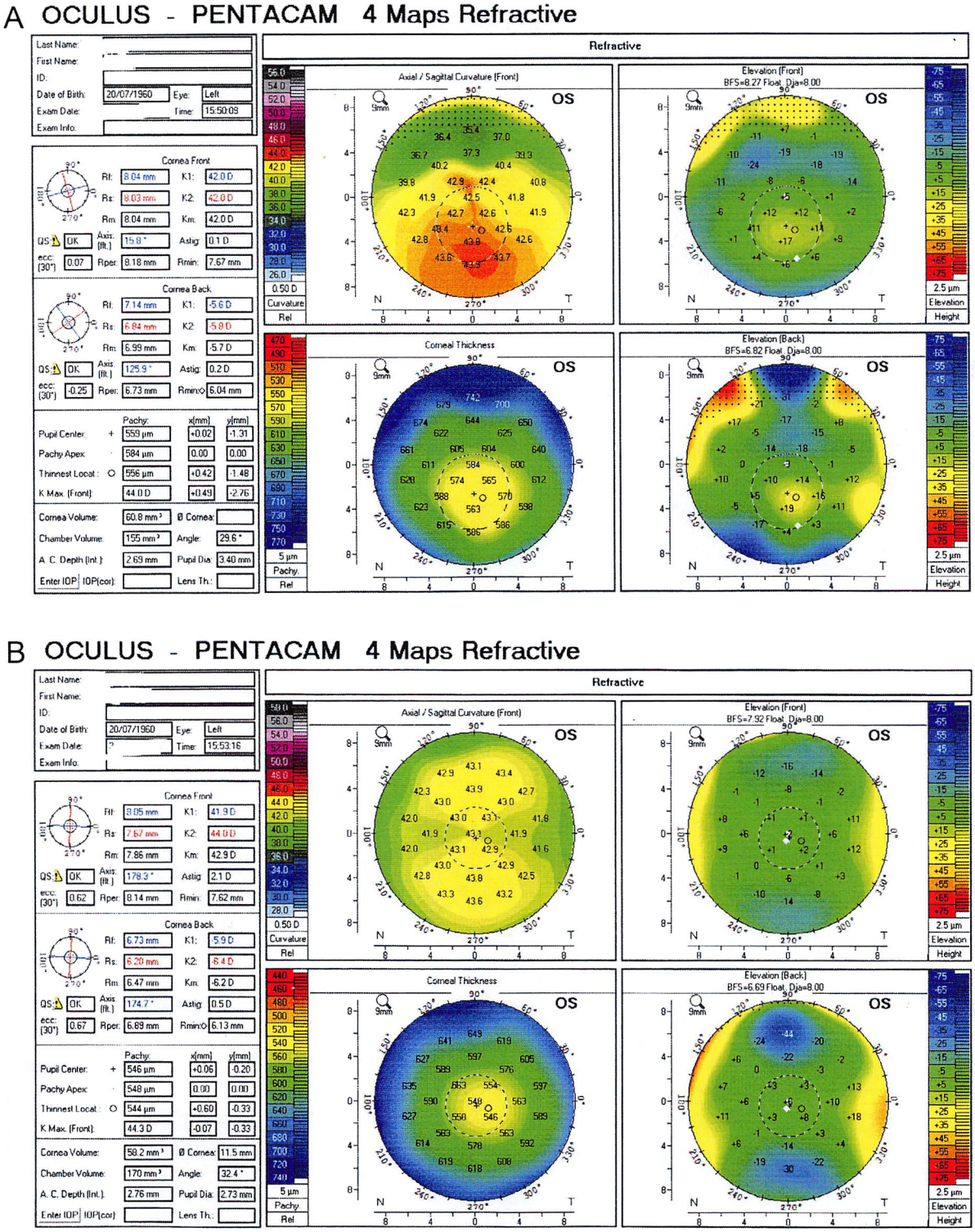

Fig. 6—A, Alignment error with the pupil decentered inferiorly on the captured image, and an inferior to superior difference of 6.6 diopters. B, Proper fixation with resolution of the high inferior to superior dioptric difference.

treated by the management of the underlying cause. Typically, the use of preservative-free tear drops, gels, ointments, enhancing humidity at home or work, and the ingestion of omega fatty acids will facilitate resolution of the SPK.

Amblyopia secondary to high astigmatism can be mistaken for keratoconus. Typically, the refractive error is stable, the anterior curvature is regular, and there is usually no posterior elevation. Best-corrected spectacle acuity with glasses or with

rigid contact lenses is reduced secondary to amblyopia. Pinhole acuity is reduced unlike with an ectatic disease.

Systemic medications may reach the cornea via the tear film, aqueous humor, and limbal vasculature. The corneal changes are often a result of the underlying chemical properties of the medication. The most common medication that can cause a whorl-like keratopathy is amiodarone.[11] This medication used for cardiac arrhythmias and is not typically used in the age group of patients with progressive ectatic disease. Nevertheless, it is important to recognize that the topographic findings may mimic an ectatic disorder. The drug can be deposited in the corneal epithelium creating an irregular topographic.[12] Elevation topography with views of the posterior cornea will be normal. Corneal thickness maps will not show any significant thinning over the steepest part of the cornea. Whorl-like or vortex keratopathy can be seen in Fabry's disease and with other systemic medications including chloroquine, amodiaquine, meperidine, indomethacin, chlorpromazine, and tomoxifen.[13]

Both rigid and soft contact lenses contact lenses can induce corneal warpage and create an irregular pattern on topography.[14–17] Corneal warpage may be secondary to mechanical action of the contact lens on the cornea or a mixed mechanism from both mechanical and metabolic changes to the corneal epithelium.[15] To differentiate keratoconus from corneal warpage it is valuable to have patients discontinue hard contact lenses for a month or longer and perform serial corneal topography or tomography. Although rare, soft contact lenses have been implicated in causing pseudokeratoconus. It is therefore important to have patients discontinue their soft lenses for approximately 1 week and repeat the corneal imaging. Progressive corneal thinning is not a diagnostic sign of corneal warpage from contact lenses.

Measurement error on topography or tomography can create a false ectasia pattern.[15–19] Patient fixation as much as 5 degrees below from the central axis of the videoscope will produce a pattern of inferior steepening.[20–21] Analysis of the pupil position in these maps will detect the centre of a pupil that is inferior to the centre of the topographic map. Repeat mapping with proper patient fixation and alignment will produce a normal pattern on corneal imaging.

Central steepening can be seen after hyperopic LASIK or PRK. A decentered hyperopic ablation is more likely to create confusion of possible ectasia. The finding of a focal area of steepening on anterior curvature topography or anterior elevation tomography can be mistaken for corneal ectasia. Differentiation from keratoconus can be aided by the lack of significant posterior elevation on tomography.

Focal areas of significant epithelial ingrowth can create corneal surface irregularity and a keratoconus pattern. This finding is not associated with posterior elevation using Scheimpflug corneal tomography and is clearly visible with slit lamp examination. Complete removal of the epithelial ingrowth may cause resolution of the irregular astigmatism unless there are permanent structural changes to the flap and or bed from melting or scarring.

New innovations in diagnostic equipment such as the use of corneal epithelial thickness mapping by anterior segment optical coherence tomography (OCT) can detect corneal epithelial topographic asymmetry, which is a sensitive tool for early and advancing keratoconus. This testing may further help in differentiating a normal eye from those with ectatic disease.[22,23]

Summary

Development of new surgical interventions for ectatic diseases has made it critical to make an accurate diagnosis so that patients receive proper counselling and treatment. The correct diagnosis of a nonectatic cornea and its etiology is made by corneal tomography and a complete ophthalmic examination. Findings of anterior curvatures changes but without significant posterior elevation on tomography are suggestive of a nonectatic cornea. New innovations such as anterior segment OCT imaging of the corneal epithelial topography may be of value in differentiating ectatic disease from a normal cornea. Slit lamp examination may allow the clinician to identify the underlying cause of corneal steepening and allow for a diagnosis of a nonectatic disease. Findings that may appear similar to ectatic disease on anterior elevation or curvature topography include SPK, whorl-like keratopathy, EBMD, focal scars, and corneal warpage from contact lenses. Amblyopia should always be suspected in patients with stable refractions, high regular astigmatism, and reduced acuity. A measurement alignment error can be detected on topography or tomography by noting a decentered pupil on imaging. It is important that ophthalmologists differentiate a nonectatic disease from ectasia to prevent unnecessary treatments of CXL as well as TG-PRK and ICR.

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Footnotes and Disclosure:

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