Excimer laser exacerbation of Avellino corneal dystrophy

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We review the clinical, histopathological, and ultrastructural findings and DNA phenotyping of a patient with Avellino corneal dystrophy exacerbated by laser in situ keratomileusis. The findings are reported and interpreted in the context of a literature review. The case highlights the possible difficulty of recognizing subtle dystrophic findings, as well as the importance of avoiding refractive surgical intervention in patients with Avellino corneal dystrophy to avoid exacerbation of dystrophic deposits in the cornea and subsequent reduction in vision.

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Avellino corneal dystrophy (ACD) exacerbation has been described after phototherapeutic keratectomy (PTK) and laser in situ keratomileusis (LASIK).[1–6] This relatively rare autosomal dominant corneal dystrophy was first reported in 1988 in individuals from Avellino, Italy[7]; however, it is now found worldwide.[8,9]

Avellino corneal dystrophy is characterized by hyaline and amyloid corneal stromal deposits, features of granular corneal dystrophy and lattice corneal dystrophy, respectively. Cases of ACD have the potential for variable phenotypic expression in affected individuals because of the differential distribution of hyaline and amyloid deposition in the corneal stroma. Hyaline deposition often occurs with earlier onset and more abundance than amyloid deposition, leading to a common misdiagnosis of granular corneal dystrophy. Despite the difference, corneal histopathology may demonstrate both deposits with appropriate staining techniques at any point during the clinical course.

Previous reports of exacerbated ACD following LASIK include Korean patients and one North American patient.[1–6] We report a case of heterozygous Avellino corneal dystrophy exacerbated by LASIK in a white North American; penetrating keratoplasty (PKP) was eventually required. Diagnostic confirmation was obtained with corneal histopathology, electron microscopy, and genetic DNA analysis. To our knowledge, this is the first description of corneal button histopathology in a patient with ACD after LASIK. The case did not require institutional review board approval and was compliant with the Health Insurance Portability and Accountability Act. Informed consent was obtained for surgical intervention and genetic analysis.

CASE REPORT

A 35-year-old white man from the United States was referred for bilateral LASIK to correct moderate myopia. The preoperative best corrected visual acuity (BCVA) was 20/20 in both eyes, with a refraction of −5.75 in the right eye and −6.50 in the left eye. A complete preoperative ophthalmic examination was normal, with the exception of several fine, subepithelial, punctate corneal opacities in both eyes. The corneal opacities were faint, of unknown etiology, and considered inconsequential. The patient denied trauma, previous ocular abnormalities, and known family history of ophthalmic disease. No Italian or Asian ancestry was present in the family tree. Corneal topography was normal in both eyes.

Bilateral LASIK surgery was performed (S.M.H.) using an Amadeus keratome (AMO) and the LadarWave CustomCornea platform (Alcon Surgical). The patient had an uneventful postoperative course and was 20/16 in both eyes at the 6-month examination. At that time, the patient was noted to have asymptomatic interface debris in both corneas, which did not affect the vision. The examination was normal otherwise.

Three years postoperatively, the patient was referred back with complaints of decreased visual acuity and a finding of increased corneal stromal opacities in both eyes (Figure 1, *A* and *B*). At that time, the BCVA was $20/25^{-2}$ in the right eye with

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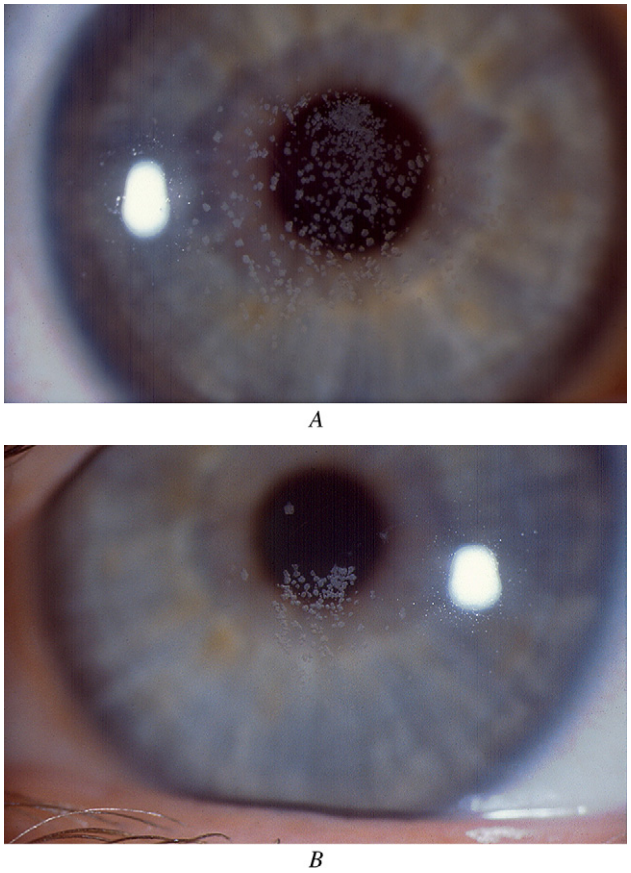

Figure 1. *A*: Slitlamp photograph of the right eye showing exacerbated ACD 3 years after LASIK. *B:* Slitlamp photograph of the left eye showing a milder case of exacerbated ACD 3 years after LASIK.

a refraction of −1.50 sphere and 20/15 in the left eye with a refraction of −0.25 +0.25 × 89. Corneal opacities with a "snowflake" appearance were noted in the LASIK flap interface and the anterior stroma, greater in the right eye than in the left eye. At that time, a family history of granular corneal deposits in the father, paternal aunt, and paternal half-brother was reported. A presumed clinical diagnosis of granular corneal dystrophy or ACD was made. The preoperative fine subepithelial opacities and postoperative interface debris were, in retrospect, consistent with dystrophic subepithelial and stromal deposits. Three months later, the BCVA in the right eye declined to 20/80 and a flap lift with scraping of the stromal bed was performed. The granular deposits in the interface were removed with scraping, but deeper stromal opacities beyond the interface depth could not be removed. Postoperatively, the BCVA improved to 20/25.

At 1 year, the patient returned with worsening of the corneal opacities, increased glare, and decreased BCVA in the right eye. A PKP was performed to eradicate the symptoms and clear the visual axis. Pathologic examination of the corneal button demonstrated a 120 µm anterior corneal flap with extensive eosinophilic granular deposits at the flap interface. The deposits were highlighted by Masson's trichrome stain (Figure 2, *A* and *B*), confirming hyaline material; Congo red stain showed a few areas of amyloid (Figure 2, *C*). Electron microscopic findings demonstrated clusters of

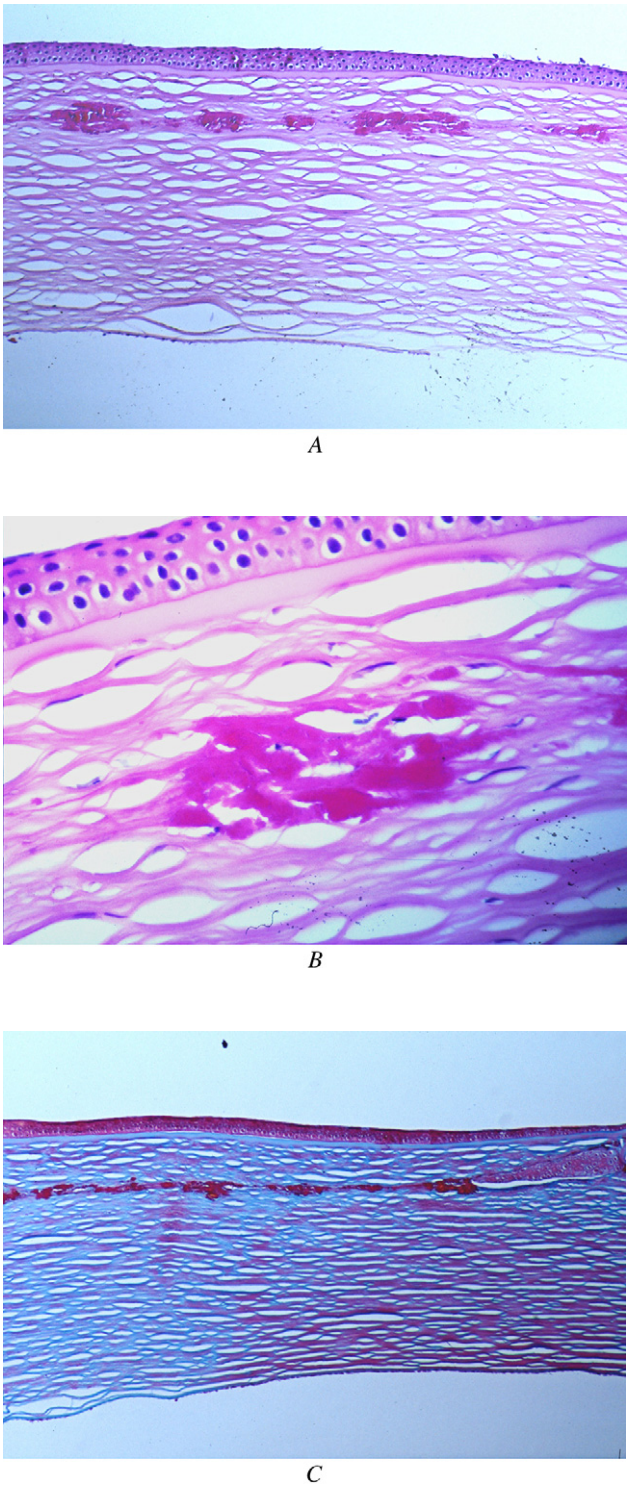

Figure 2. *A:* Low-magnification view depicting Congo red staining of amyloid deposits in ACD within the LASIK flap interface obtained by sectioning the corneal button following PKP. *B:* High-magnification view depicting Congo red staining of amyloid deposits in ACD exacerbated by LASIK. *C:* Low-magnification view depicting Masson's trichrome staining of hyaline deposits in ACD exacerbated by LASIK.

electron-dense granular material present at the LASIK flap interface and in the anterior stroma along with multiple rectangular- to rhomboidal-shaped electron-dense structures that were interpreted as consistent with granular dystrophy (Figure 3). Genetic DNA analysis of the patient's whole blood using the Gentra Puregene DNA Isolation Kit demonstrated a heterozygous R124H mutation specific for ACD, confirming the diagnosis of ACD rather than granular dystrophy.

At 8 months, the graft remained clear with no recurrence of granular opacities. The BCVA measured $20/20^{+2}$ with a refraction of $-7.25 + 3.00 \times 85$. The left eye remained 20/25 with persistent asymptomatic stromal opacities.

Results of the Literature Review

A literature search for reports of Avellino corneal dystrophy was cross-matched with excimer laser treatment of the cornea including PTK, photorefractive keratectomy (PRK), and LASIK. A review of the findings is shown in Table 1.

Twenty patients (32 eyes) had excimer laser exacerbation of ACD. Including our report, 9 patients (17 eyes) had a recurrence of ACD after LASIK; 7 from Korea[3] and 2 from the U.S.[6] Eleven patients (15 eyes) had a recurrence after PTK; 10 from Japan[1,4] and 1 from Korea.[18] All but 1 patient had documented preoperative corneal opacities; in 1 patient, it was not clear whether opacities were present. The mean age of the patients was 44 years (range 22 to 78 years). The mean time of ACD exacerbation after an excimer laser ablation procedure was 26 months (range 3 months to less than 5 years). The mean best corrected visual acuity (BCVA) after excimer laser ablation and ACD exacerbation was 20/50 (range 20/20 to 20/500). One patient had PKP.

Of the patients who developed ACD after LASIK, 8 had documented preoperative corneal opacities and 1 was suspected of having corneal opacities prior to LASIK. Significant recurrences occurred from 6 months to less than 5 years after LASIK. In 8 patients, the BCVA decreased as a result of an accumulation of dystrophic material in the corneal stroma.[3,6] Similarly, our patient had preoperative corneal opacities that were mistakenly considered inconsequential given the initial negative family history, limited number of deposits, and atypical appearance. He developed a significant exacerbation of dystrophic material between 2 years and 3 years after bilateral LASIK.

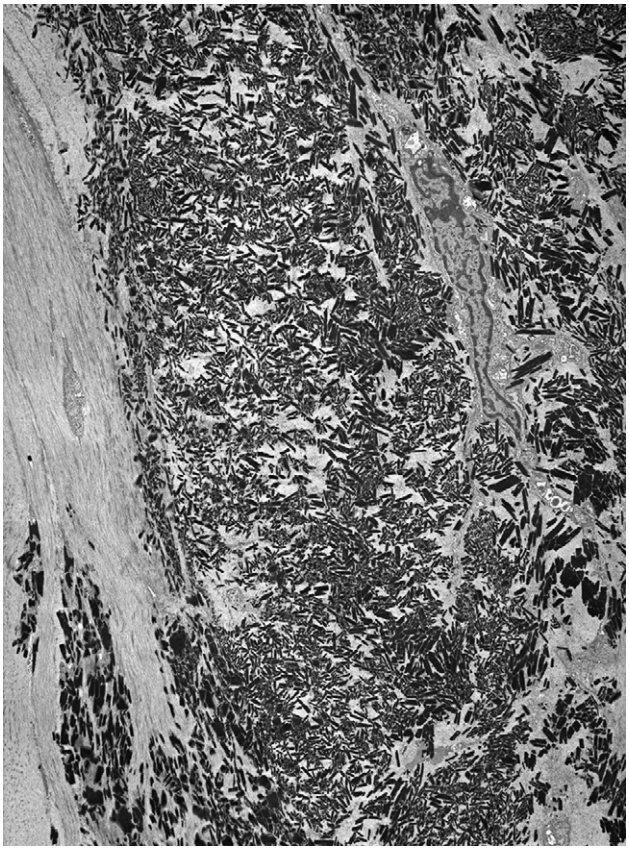

Figure 3. Electron microscopy in ACD showing a cluster of electron-dense granular material present at the LASIK flap interface in the anterior corneal stroma, with multiple rectangular- to rhomboid-shaped electron-dense structures.

DISCUSSION

Avellino corneal dystrophy, typically diagnosed by clinical and phenotypic characteristics, can now be effectively classified by genetic DNA analysis. Our case demonstrates the phenotypic similarities between ACD and granular corneal dystrophy, which can lead to diagnostic confusion, especially early in the clinical course. Because there were no characteristic clinical findings of amyloid deposition in the cornea, the case looked very similar to granular corneal dystrophy clinically. In fact, the electron microscopy results also resembled granular dystrophy; ie, an absence of deposits with the parallel packing of fibrils associated with fusiform amyloid deposits, as described elsewhere.[6,11] Genetic analysis confirmed the specific point mutation in the nucleotide sequence CGC to the nucleotide sequence CAC, which leads to replacement of histidine by arginine at codon 124 on the transforming growth factor (TGF)-β–inducing gene, also known as the TGF-β1 (BIGH3) gene, on chromosome 5q (Arg124His or R124H). This point mutation differentiates ACD from other dystrophies associated with mutations of the TGF-β1 gene.[12–15] Our patient was found to carry a heterozygous mutation rather than a homozygous mutation, a possible modifier leading to the subtle nature of corneal findings prior to LASIK.

The DNA analysis was crucial in confirming the diagnosis in our case. While corneal histopathology demonstrated Masson's trichrome staining consistent with hyaline material and Congo red staining indicative of amyloid deposits, both of which are hallmarks of ACD, electron microscopic findings appeared more consistent with granular corneal dystrophy. Amyloid deposition is not unique to ACD and is commonly found as a degenerative deposit in conditions such as secondary localized amyloidosis. Without DNA analysis, a diagnosis could not be definitively established,

Table 1. Cases of ACD exacerbated by excimer laser applications to the cornea.

Author*	Patient	Age (Y)	Origin	Eyes Treated
Kim[18]	1	30	Korea	1 (RE)
Dogru[10]	1	63	Japan	1
	2	78	Japan	1
	3	62	Japan	1
Inoue[5]	1	30	Japan	1 (LE)
	2	31	Japan	2 (RE) (LE)
	3	60	Japan	1 (RE)
	4	64	Japan	1 (RE)
	5	59	Japan	2 (RE) (LE)
	6	67	Japan	2 (RE) (LE)
	7	74	Japan	2 (RE) (LE)
Jun[3]	1	27	Korea	2 (RE) (LE)
	2	22	Korea	1 (LE)
	3	28	Korea	2 (RE) (LE)
	4	32	Korea	2 (RE) (LE)
	5	27	Korea	2 (RE) (LE)
	6	27	Korea	2 (RE) (LE)
	7	22	Korea	2 (RE) (LE)
Banning[6]	1	25	USA	2 (RE) (LE)
Lee (current study)	1	35	USA	2 (RE) (LE)

BCVA = best corrected visual acuity; LASIK = laser in situ keratomileusis; LE = left eye; PTK = phototherapeutic keratectomy; RE = right eye
*First author

further emphasizing the importance of genotyping corneal dystrophies. Our case demonstrated electron microscopic findings previously reported in granular dystrophy cases but failed to show signs of lattice dystrophy, probably a result of the relative sparsity of amyloid commonly seen in early ACD. Electron microscopy showed multiple granular opacities at the LASIK flap interface, as seen in previous electron microscopy studies.[16] The similarities between granular dystrophy and ACD clinically and ultrastructurally underscore the necessity of genetic analysis over other diagnostic methods for confirmation of a diagnosis. This diagnostic confusion becomes important when considering the dramatic differences in response to PTK treatment depending on the particular corneal dystrophy.

Several reports describe successful removal of the deposits of ACD and other corneal dystrophies using PTK to delay PKP.[1,10,17] Dinh et al.[17] describe successful PTK in 43 eyes, 20 of which represented lattice or granular corneal dystrophy. Dogru et al.[10] note favorable effects of PTK in 29 eyes with ACD or granular corneal dystrophy. Phototherapeutic keratectomy combined with mitomycin-C application reduced corneal stromal opacities and improved visually acuity in 4 patients with ACD for at least 1 year.[18] Despite these favorable initial results, PTK recurrence continues to remain an issue, as illustrated by recurrences in 20% of the 20 eyes reported by Dinh et al.[17] and 5 of the patients reported by Dogru et al.[1] in follow-up studies. In fact, Dogru et al.[1] noted that recurrences were more confluent and dense and associated with increased opacification than in primary dystrophic cases, an observation which raises concern about PTK treatment in ACD.

Table 1 (cont.)

Procedure	Excimer Laser	Preop Deposits	Recurrence-free Interval (Mo)	Post-Procedure BCVA
PTK	B & L Technolas 217z	Yes	3	20/500
PTK	Nidek EC-5000 (all cases)	Yes	9	20/32
PTK		Yes	7	20/25
PTK		Yes	7	20/25
PTK	Visx 20/20 (all cases)	Yes	13	20/33
PTK		Yes	11	20/33
PTK		Yes	12	20/40
PTK		Yes	5	20/40
PTK		Yes	38	20/40
PTK		Yes	44	20/22
PTK		Yes	49	20/20
PTK		Yes	37	20/50
PTK		Yes	30	20/25
PTK		Yes	35	20/67
PTK		Yes	36	20/50
LASIK	Mel 60	?	14	20/30
LASIK		?	14	20/50
LASIK	Visx 20/20	Yes	<5 y	20/100
LASIK	Visx S2	Yes	<4 y	20/40
LASIK		Yes	<4 y	20/20
LASIK	Nidek EC-5000	Yes	<2 y	20/20
LASIK		Yes	<2 y	20/20
LASIK	Telco	Yes	13	20/30
LASIK		Yes	13	20/30
LASIK	Visx S2	Yes	12	20/25
LASIK		Yes	12	20/25
LASIK	Kerator 217	Yes	12	20/30
LASIK		Yes	12	20/30
LASIK	Not specified	Yes	6	20/20
LASIK				20/20
LASIK	Alcon LadarWave 4000	Yes	36	20/70 20/20 (PKP)
LASIK		Yes	36	20/20

One study,[5] which describes a recurrence of ACD in 7 patients following PTK, suggests that the clinical features and recurrence-free interval following treatment depend on whether the patient has a homozygous or heterozygous R124H mutation. This study found that recurrences in heterozygous patients were indolent, more superficial, and had smaller and less discrete white granular deposits, whereas homozygous patients demonstrated a more rapid centripetal spread with increased depth of penetration, size, and density. Our heterozygous patient typified this description in both clinical presentation and the interval between excimer laser treatment and exacerbation. Manipulation of the cornea, specifically lifting the flap and scraping the stromal bed, temporarily improved symptoms and vision but ultimately led to more extensive stromal material deposition and required PKP. Other authors hypothesize that the ocular surface and stromal insult associated with PTK, PRK, and LASIK results in increased deposition of dystrophic materials in patients with ACD.[1–3] Hence, we theorize that increased keratocyte stimulation from tissue manipulation can lead to a clinical appearance more typical of a patient with homozygous R124H mutation for ACD.

Our case illustrates several issues highlighted in previous reports of ACD worsened by LASIK and PTK. Specifically, corneal stromal deposition of dystrophic material occurs more extensively and rapidly after excimer laser corneal ablation. Animal studies[19,20] show that excimer laser application to rat corneas induces a stressful injury to the corneal stroma, thereby promoting upregulation of TGF-β genes. Induction of these genes promotes increased synthesis of cytokines, stromal glycosaminoglycans, and extracellular matrix proteins in response to tissue injury. Keratocyte stimulation resulting from these stress-induced cellular changes may represent the stimulus leading to

deposition of abnormal material in ACD following excimer laser treatment to the cornea. This may explain why increased corneal deposits were seen at the flap interface within the central corneal treatment zone on the histopathology of our patient's corneal button. Additional studies[19,20] found a similar increase in deposition of dystrophic material in the LASIK flap interface. Lifting the LASIK flap and scraping the stromal bed may eliminate some of the material and result in improved visual acuity, as seen in our case initially; however, the accumulation of abnormal material will continue and may be worsened by any intervention that results in corneal stress and resulting keratocyte activation. Again, this factor raises concern about the use of PTK in primary cases of ACD. Although PTK may provide short-term improvement, it may lead to more aggressive recurrences of ACD than in cases of granular dystrophy.

This case emphasizes the need to avoid excimer laser treatment in ACD corneas. While short-term visual needs may be met, long-term outcomes will not be satisfactory, as illustrated by our patient who required PKP in 1 eye. A literature review raised additional concerns about PTK in cases of ACD, as the potential for more aggressive recurrences may exist. Phototherapeutic keratectomy with mitomycin-C has shown initial success in a small group of patients with ACD, but longer follow-up and more studies are needed before this recommendation can be accepted for routine ACD treatment. Genetic analysis may be beneficial in the differentiation between ACD and granular dystrophy. This differentiation has significant implications for treatment because of the tendency for ACD to worsen with excimer laser or mechanical manipulation.

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