

Multiple excimer laser phototherapeutic keratectomies for Avellino corneal dystrophy: a case report

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Dear Editor,

I am Chihiro Koiwa, from the Department of Ophthalmology, Juntendo University Hospital. I am writing this letter to present a case of multiple excimer laser phototherapeutic keratectomies (PTKs) for Avellino corneal dystrophy (ACD). Corneal dystrophy is a common type of hereditary, non-inflammatory, and bilateral corneal disorder that involves various pathological, histological, and clinical manifestations^[1]. Advanced molecular gene sequencing has identified specific mutations that are associated with most dystrophies of this type. ACD, also known as granular corneal dystrophy type II^[2], is autosomal dominant and associated with the R124H mutation of the transforming growth factor beta-induced (*TGFBI*) gene and characterized by deposits consistent with both discrete granular and lattice corneal opacities^[3-4]. An analysis of the *TGFBI* gene is essential to differentiate ACD because heterozygous R124H mutation carriers have minimal corneal abnormalities, whereas homozygotes have severe visual impairment, starting from early childhood, and early postoperative recurrence of corneal opacity.

Excimer laser PTK has been widely performed to treat anterior stromal opacity in ACD^[4]. Conversely, deep anterior lamellar keratoplasty and penetrating keratoplasty are applicable when corneal opacity spreads to the deep stroma. Previous studies have reported that PTK for ACD has good clinical outcome in terms of improving visual acuity; however, the recurrence of corneal opacity after PTK cannot be completely prevented^[4-6]. Inoue *et al*^[6] reported that the recurrence-free intervals after PTK in ACD were 9.5±3.1mo for the homozygotic form and 38.4±6.3mo for the heterozygotic form. PTK does not remove the cells that produce abnormal proteins but cleaves the intermolecular protein bonds and resects the opacity of the corneal surface layer. Although re-PTK treatment for ACD is considered effective as long as the corneal bed remains, few case studies have reported multiple PTK applications^[6-8]. This report presents the case of a patient with ACD with homozygous R124H mutation who underwent PTK nine times for recurrence of corneal opacity to both eyes during a 35-year follow-up period. The study was approved by the Independent Ethics Committee at Juntendo University Hospital (Approval number, JHS 19-009) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Case Presentation The patient was a 44-year-old Japanese man. Whitish corneal opacities were first noticed in both his eyes when he was 3 months old. He was the offspring of a consanguineous marriage. He was referred to Juntendo University Hospital, Tokyo, Japan for treatment of his corneal disorder at the age of 6y (September 1979); at that time, his best-corrected visual acuity (BCVA) was 10/20 in the right eye and 8/20 in the left eye. Slit-lamp examination showed bilateral dense nodular epithelial and round anterior stromal opacities. We previously reported DNA sequencing results for this patient showing homozygosity for the *TGFBI* gene R124H (CGC→CAC) mutation; diagnosing this mutation differentiates ACD from other dystrophies associated with mutations of the *TGFBI* gene^[3]. Keratectomy was performed five times in the right eye and three times in the left eye by the time he was 12 years old. When he was 21 years old (October

1994), he underwent primary PTK in his left eye due to severe recurrence of corneal opacity, and then he underwent primary PTK on the right eye when he was 30 years old (October 2003). At his primary PTK, his BCVA was 20/2000 in the right eye and 20/100 in the left eye, and corneal thickness was 584 μm in the right eye and 600 μm in the left eye. PTK was performed using a Quest excimer laser (NIDEK Co., Ltd. Gamagori, Aichi, Japan). The ablation zone was set at 6 mm as the optical zone and 7 mm as the transition zone. He underwent a second PTK on his right eye on February 2005 (Figure 1) and on his left eye on December 2000 due to decreased BCVA with severe recurrence. After the second PTK, opacities were removed and BCVA increased to 20/20 in the right eye and to 20/16 in the left eye. Since corneal opacities recurred, PTK was performed five times on his right eye between 2003 and 2017 with 580 μm of the total amount of corneal ablation, and four times on his left eye between 1994 to 2011 with 570 μm of the total amount of corneal ablation (Figure 2). The average recurrence-free interval was $8.9 \pm 4.4\text{mo}$ in the right eye and $9.6 \pm 4.0\text{mo}$ in the left eye in this case. Figure 3 shows the trend of visual acuity. The BCVA improved after every PTK.

At his last visit, in December 2018, due to disease recurrence on the ablation zone (Figure 4A, 4B), BCVA had decreased to 20/25 in the right eye and to 20/66 in the left eye. Astigmatism was observed in the last visit, but there was no marked change in refraction. Corneal thickness was 509 μm in the right eye and 525 μm in the left eye using an ultrasonic pachymeter (SP-100, Tomey Corporation, Nagoya, Aichi, Japan). Anterior segment optical coherence tomography (SS-1000, Tomey Corporation) images showed that the opacity thickness was 103 μm in the right eye and 149 μm in the left eye (Figure 4C, 4D). Topography (TMS-4, Tomey Corporation) showed no signs of keratectasia (Figure 4E, 4F). Corneal endothelial cells could not be counted regularly (EM-3000, Tomey Corporation) because the opacities were numerous and in close proximity, but there was no decrease in corneal endothelial cells at the course of 10y so far as we could measure (Figure 4G).

Data Analysis The criteria for recurrence were set according to a previous study^[5]. Briefly, recurrence of ACD was considered when there were slit-lamp signs of recurrent corneal opacity with significant visual loss. The correlations between the ablation volume and the recurrence-free interval and re-PTK intervals were analyzed by Pearson's correlation coefficient with the measurements at each PTK comprising the sample ($n=9$) using GRAPHPAD PRISM (GraphPad Software, San Diego, CA, USA). Data are presented as mean \pm standard deviation (SD).

DISCUSSION

ACD advances corneal opacity with aging and reduces visual acuity. It is considered that PTK is an effective treatment for

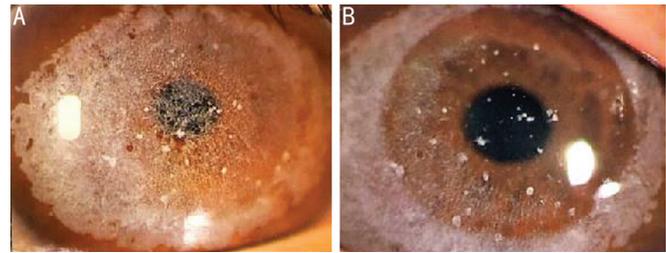


Figure 1 Representative slit-lamp photographs between pre- and post-excimer laser PTK in Avellino corneal dystrophy The slit-lamp photographs are pre-second PTK (A) and post-PTK (B) on the right eye.

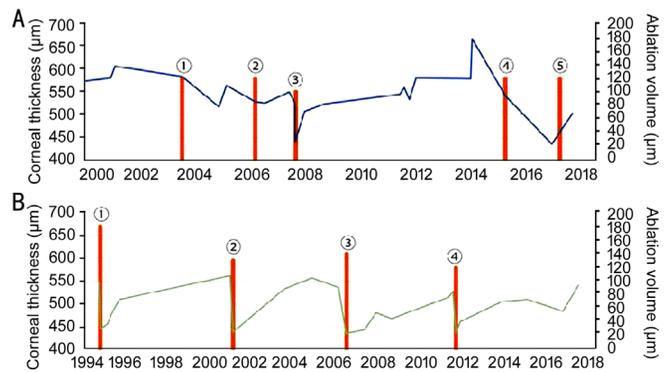


Figure 2 Trends of central corneal thickness after phototherapeutic keratectomy The line graph shows the trend of corneal thickness for the right eye (A) and for the left eye (B). The bar graph shows the ablation volume of excimer laser phototherapeutic keratectomy on the right axis.

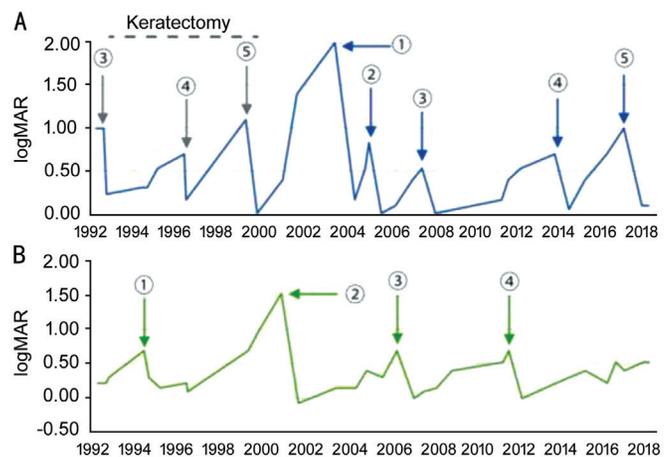


Figure 3 Trends of visual acuity after phototherapeutic keratectomy The line graph shows the trend of visual acuity for the right eye (A) and for the left eye (B). Gray arrow: keratectomy, blue arrow excimer laser PTK on the right eye, and green arrow: PTK on the left eye.

corneal opacity; however, corneal opacity recurs numerous times in ACD homozygotic cases. This report describes the case of a patient who underwent PTK nine times (five on the right eye and four on the left eye) over the course of 35y, suggesting the effectiveness of re-PTK for the recurrence of ACD.

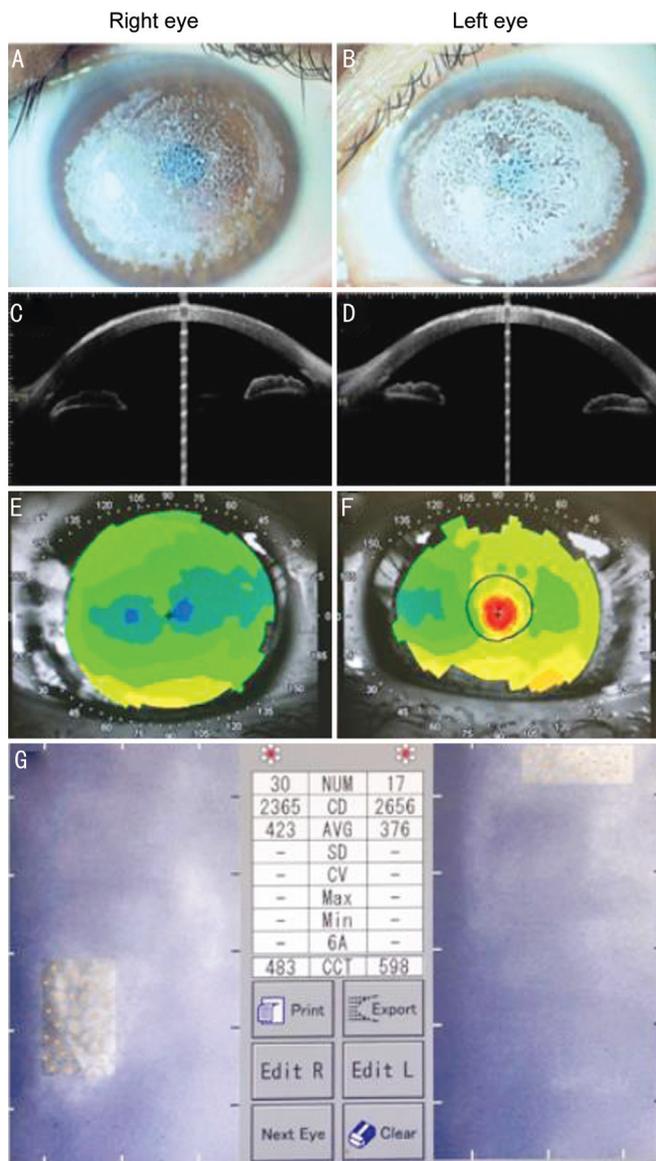


Figure 4 Last visit examinations Slit-lamp photographs show a large number of gray-white granular opacities in the superficial stroma (A, B). Anterior segment optical coherent tomography shows corneal opacity at the superior stroma (C, D). Topography shows no signs of keratectasia (E, F). Specular microscopy shows no decrease in endothelial cell density (G).

As in this case, if the corneal opacity occurs at the center of the pupil area and causes decreased visual acuity, it becomes an indication for treatment including PTK and corneal transplantation. Re-PTK led to visual acuity improvement as shown in Figure 3, and there was no change in corneal endothelial cell density as shown in Figure 4G. Therefore, PTK was less invasive to corneal tissue, involved a shorter operation time compared to corneal transplantation, and reoperation could be easily performed at recurrence, indicating that PTK may be an effective and therapeutic treatment method for the recurrence of ACD.

Previous studies have reported that younger age, homozygous mutation of R124H, corneal refractive surgery including

photorefractive keratectomy and laser-assisted *in situ* keratomileusis, and deep ablation depth are risk factors of recurrence of corneal opacity in ACD^[9-10]. This study reported that the average recurrence-free interval was 8.9±4.4mo with an average amount of ablation 116±8.9 μm in the right eye, and 9.6±4.0mo with an average amount of ablation 142.5±26.3 μm in the left eye, which were similar to the values measured in previous cases with homozygous ACD (9.5±3.1mo with average amount of ablation, 90.0±20.0 μm)^[6]. In this case, there was no correlation between the amount of resection and the period of recurrence ($r=0.108$, Pearson's correlation coefficient), and the number of PTK applications did not affect the period of recurrence, indicating that even if multiple PTKs are performed, the period of recurrence will not be affected. Multiple PTKs did not cause keratectasia, with the corneal bed thickness remaining unaffected, and did not reduce corneal endothelial cell density (Figure 2 and Figure 4G), suggesting that multiple PTKs could be repeatedly performed as an effective and safe treatment for ACD recurrence. It could also be speculated that the corneal bed thickness was restored after multiple PTKs due to corneal re-epithelization in the light of abnormalities of the epithelial basement membrane (Figure 4C, 4D) and corneal wound remodeling of the anterior corneal stroma owing to the condition's inherent recurrence nature^[11-12]. In summary, we described the case of a patient with ACD who underwent PTK nine times during 35y of long-term observation. It is suggested that resection of corneal opacity by re-PTK may be an effective and safe treatment against recurrence of corneal opacity in ACD.

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Conflicts of Interest: Koiwa C, None; Nakatani S, None; Inomata T, None; Yamaguchi M, None; Iwamoto S, None; Murakami A, None.

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Multiple excimer laser PTK for Avellino corneal dystrophy

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