• Letter to the Editor •

Slow granular corneal dystrophy type 2 exacerbation after SMILE: a bilateral asymmetric case resembling a unique previous unilateral case

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Dear Editor,

Granular corneal dystrophy type 2 (GCD2), an autosomal-dominant corneal stromal dystrophy[1], is exacerbated by corneal trauma, which is known to induce the transforming growth factor β (*TGF-β*) gene and the transforming growth factor β induced (*TGFBI*) gene[2]. Exacerbation of GCD2 is well known after iatrogenic trauma to the cornea by surgical refractive procedures including photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy (LASEK), and laser-assisted *in situ* keratomileusis (LASIK)[1]. Recently, small incision lenticule extraction (SMILE) was introduced as a refractive procedure that might cause less damage to the corneal epithelium than LASIK, PRK, or LASEK[3]. To date, only one case of GCD2 following unilateral SMILE has been reported, which exhibited a slow progression of the disease[4]. We report the outcome of bilateral SMILE in a patient with GCD2, which demonstrated an asymmetric exacerbation of the disease, and compare our findings with previously reported cases of unilateral SMILE and bilateral LASIK that similarly exhibited asymmetric exacerbation of GCD2. Additionally, we discuss the possible underlying pathophysiology and explore potential therapeutic approaches for the management of GCD2-affected corneas following SMILE.

Ethical Approval This study followed the tenets of the Declaration of Helsinki and was approved by Daegu Catholic University Hospital IRB (DCUMC IRB 2025-02-022) and Severance Hospital IRB (4-2012-0209, 4-2020-0600, 4-2025-0053). Written consents were obtained from the patient.

Case Presentation A 24-year-old female patient (Case 1) was referred to the ophthalmology outpatient clinic 48mo after bilateral SMILE for evaluation of corneal opacities in the left eye. Her medical history was unremarkable, with no prior corneal trauma or infections. No corneal opacities were documented on slit-lamp examination before SMILE.

Her preoperative manifest refraction was −1.50−0.75×4 in the right eye (OD) and −1.00−0.50×7 in the left eye (OS), with a corrected distance visual acuity (CDVA) of 20/20 in both eyes. At presentation, 48mo postoperatively, her uncorrected distance visual acuity (UCDVA) remained 20/20 in each eye. Slit-lamp examination revealed a single, small stromal deposit in the right cornea and approximately 312 fine granular deposits in the left cornea (Figure 1A, 1B).

At the 52-month follow-up, Fourier-domain optical coherence tomography (FD-OCT; RTvue-100, Optovue Inc., Fremont, CA, USA) demonstrated a faint hyperreflective deposit beneath Bowman's layer in the right cornea and numerous deposits along the stromal interface in the left cornea (Figure 1C, 1D, 1G, 1H). At the most recent follow-up visit, 59mo after SMILE, the right eye remained unchanged, while the left eye demonstrated mild but progressive findings, including slightly enlarged and occasionally confluent deposits (Figure 1E, 1F, 1I–1L). UCDVA remained stable at 20/20 in both eyes throughout the follow-up period.

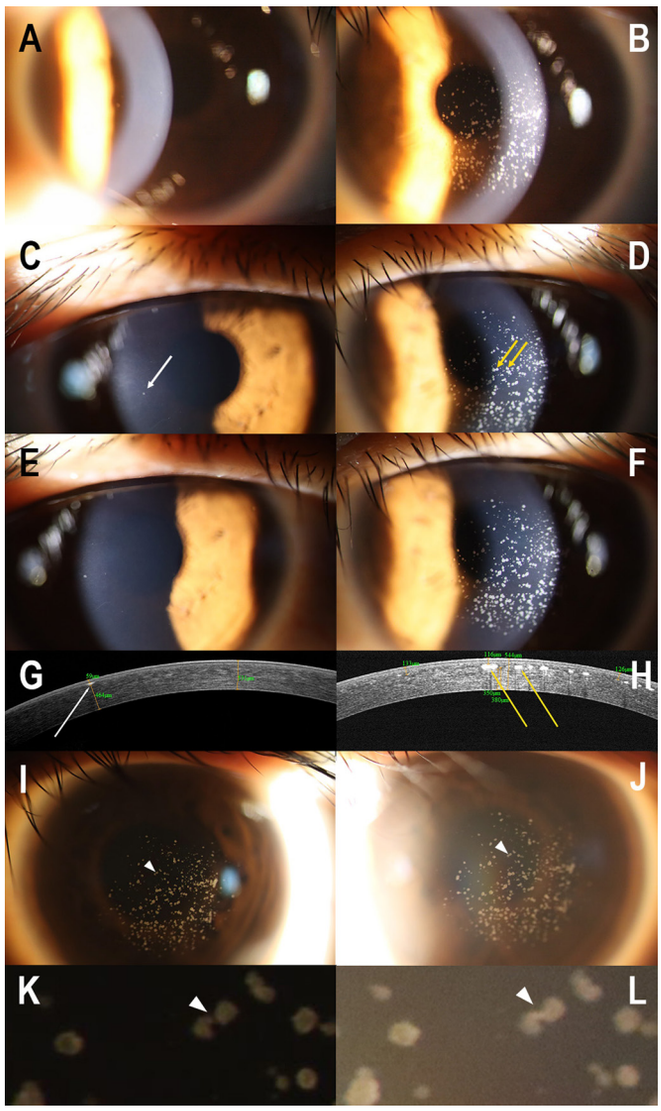

Figure 1 Corneal deposits in a heterozygous GCD2 patient (Case 1) at 48, 52, and 59mo after SMILE in both eyes A: Slit-lamp photographs of the right eye 48mo after SMILE; B: Slit-lamp photographs of the left eye 48mo after SMILE; C: Slit-lamp photographs of the right eye 52mo after SMILE; D: Slit-lamp photographs of the left eye 52mo after SMILE; E: Slit-lamp photographs of the right eye 59mo after SMILE; F: Slit-lamp photographs of the left eye 59mo after SMILE; G: FD-OCT image of the right eye confirming deposits just beneath Bowman's layer, taken simultaneously with C; H: FD-OCT image of the left eye confirming deposits at the stromal interface created by the SMILE procedure, taken simultaneously with D. White arrow in C and G and yellow arrows in D and H indicate the same deposits; I and K: Slit-lamp photographs 52mo after SMILE; J and L: Slit-lamp photographs 59mo after SMILE. Two separate faint deposits in the left eye at 52mo (I and K) became enlarged and connected at 59mo (J and L). White arrowheads indicate the same deposits. GCD2: Granular corneal dystrophy type 2; SMILE: Small incision lenticule extraction; FD-OCT: Fourier-domain optical coherence tomography.

Genetic analysis *via* full sequencing of the *TGFBI* gene identified a heterozygous R124H mutation in exon 4, confirming the diagnosis of GCD2.

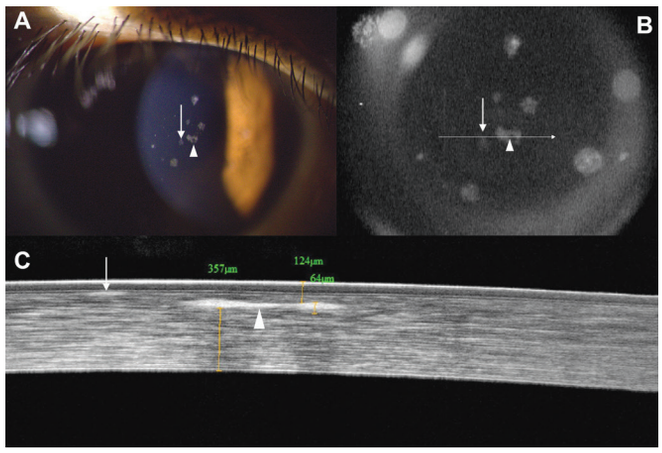

Figure 2 Corneal deposit photographs of a heterozygous GCD2 patient (Case 2) 33mo post-unilateral SMILE A: Slit-lamp photograph shows granular deposits in the right eye in the anterior stroma (arrow) and at the SMILE interface (arrowhead); B: FD-OCT video image of the right eye. The arrow and arrowhead point to deposits that are marked in A; C: FD-OCT image shows that one of these deposits is in the anterior sub-epithelial stroma (arrow), and the other is located at the SMILE interface (arrowhead). These are different photographs of the same cornea previously described, taken 33mo following unilateral SMILE[4]. GCD2: Granular corneal dystrophy type 2; SMILE: Small incision lenticule extraction; FD-OCT: Fourier-domain optical coherence tomography.

Comparative Case after SMILE To further investigate the timeline of GCD2 exacerbation following SMILE, we reanalyzed a previously published case (Case 2) from unilateral SMILE in a patient with genetically confirmed GCD2 (Figure 2). That cornea also exhibited slow progression, with no new deposits detected at the interface on FD-OCT until 33mo after SMILE[4].

Comparative Cases of Asymmetric Exacerbation following LASIK By comparing three GCD2 corneas that underwent SMILE—two from the present case and one from a previously reported unilateral case—we found that the degree of exacerbation in these SMILE-treated corneas was less pronounced than that reported after LASIK, based on multiple prior studies accompanied by clinical imaging[1].

To further compare our asymmetrically exacerbated SMILE-treated corneas with asymmetrically exacerbated LASIK-treated corneas, we analyzed four corneas from two genetically confirmed GCD2 patients (Cases 3 and 4) who presented to Severance Eye Hospital 1 and 3y after undergoing bilateral LASIK, respectively. These patients demonstrated numerous deposits in their right corneas and relatively fewer deposits in their left corneas. They were followed up for 13 and 7y postoperatively, respectively (Figure 3; Cases 3 and 4). The deposits were located along the stromal interface created

during LASIK and progressively increased in number over time in each eye, exhibiting asymmetric rates of progression. Notably, the speed of exacerbation was higher than that observed in the SMILE-treated corneas.

We report herein the corneal findings of a GCD2 patient 4y after bilateral SMILE, demonstrating no exacerbation in the right cornea and slow progression of GCD2 deposits accumulation at the SMILE interface in the left cornea. According to several previous studies, moderate to severe deposit formation leading to significant visual impairment over a relatively short period has been commonly observed following LASIK[1]. In contrast, both the corneas in our current case and the cornea in the previously reported case at 33mo post-unilateral SMILE[4] exhibited slower progression of GCD2 compared to previously reported cases of GCD2 exacerbation after LASIK.

Several reports, however, should be considered before concluding that exacerbation of GCD2 is less severe after SMILE than after LASIK. First, the severity of phenotypic expression of corneal deposits has been reported to vary widely among heterozygous GCD2 patients[5]. Second, the amount of transforming growth factor beta-induced protein (TGFBIp), which is predominantly produced in the corneal epithelium, varies greatly among the corneal epithelium of healthy individuals[5]. Third, as Choi *et al*[6] observed a twofold variation in the expression levels of 555 genes between primary cultured wild-type and homozygous GCD2 corneal fibroblasts, unidentified genetic interactions between the GCD2 gene and other genes may influence the severity of GCD2 phenotypes[6]. These findings highlight the challenges in determining the exact impact of SMILE on phenotypic variations based on only three cases, and the underlying mechanisms controlling TGFBIp production require further investigation.

Should a difference in the exacerbation of GCD2 between SMILE and LASIK exist, it may be explained by differences in corneal epithelial injury, which is less extensive with SMILE than with LASIK. Corneal deposits in patients with GCD2 exacerbation after LASIK are known to contain mutated TGFBIp[7]. Given that TGFBIp production is regulated by levels of TGF-β, which are upregulated during the wound-healing process[1], and that corneal epithelial cells produce greater amounts of TGFBIp than stromal keratocytes[7-9], it is reasonable to hypothesize that the amount of TGFBIp deposits generated after SMILE would be lower than that after LASIK. However, the asymmetry observed between the two eyes in our case does not fully support this hypothesis and suggests that additional factors contribute to the variability in GCD2 progression after SMILE.

There are several possible explanations for what appear to be less frequent and less severe exacerbations of GCD2 after SMILE than after LASIK. First, compared with LASIK, SMILE involves a smaller stromal incision, potentially leading to less stromal injury and, consequently, a smaller area of keratocyte damage after SMILE than after LASIK[10]. Second, earlier reports of GCD2 exacerbation after LASIK may be attributable to less consistent flap thickness and greater stromal injury associated with mechanical microkeratomes, in contrast to more recent laser procedures in femtosecond LASIK[11] or SMILE. It remains to be determined whether the incidence and/or severity of GCD2 exacerbation after femtosecond LASIK and SMILE would be different if the depth of incisions for the two procedures were comparable.

Signs of recurrence were not observed in the right cornea, whereas multiple very fine deposits were present in the left cornea in our bilateral SMILE case. The left cornea exhibited a definite, albeit slow, progression of deposit accumulation at the stromal interface, as demonstrated by comparative photographs taken at 52 and 59mo after SMILE (Figure 1I–1L). We also presented two additional LASIK cases (Figure 3; Cases 3 and 4), in which the right eyes exhibited severe exacerbation of GCD2, while the fellow left eyes demonstrated an unusually delayed recurrence. Despite the initial delay, the left eyes eventually developed an increased number of deposits indicative of GCD2 exacerbation after an extended postoperative period. Based on the asymmetric progression observed in the LASIK cases, we speculate that the right cornea in our SMILE case may also eventually develop deposits at the stromal interface, although a longer follow-up period may be necessary.

No effective or universally accepted treatment strategy has yet been established for managing recurrences of GCD2 following corneal refractive surgery. In patients with exacerbation of GCD2 following LASIK, keratoplasty can be delayed by performing phototherapeutic keratectomy (PTK) to remove superficial deposits. A report of PTK treatment after LASIK showed that flap amputation and removal resulted in significantly better visual recovery and less severe deposits compared to flap conservation 36mo after procedures[7]. If the concept of PTK on the remaining posterior stroma were applied to SMILE cases, one possible approach would be to excise the anterior portion of the cornea at the SMILE-induced interface and then perform PTK on the remaining posterior stromal surfaces either with the flap removed or repositioned[7]. Additionally, as suggested by previous SMILE case, another SMILE procedure could be performed to remove the lenticule containing the deposits for therapeutic purposes[4], although recurrence may occur and there is a risk of complications such as buttonhole formation in the anterior stroma and Bowman's layer, particularly when the stroma anterior to the interface is thin.

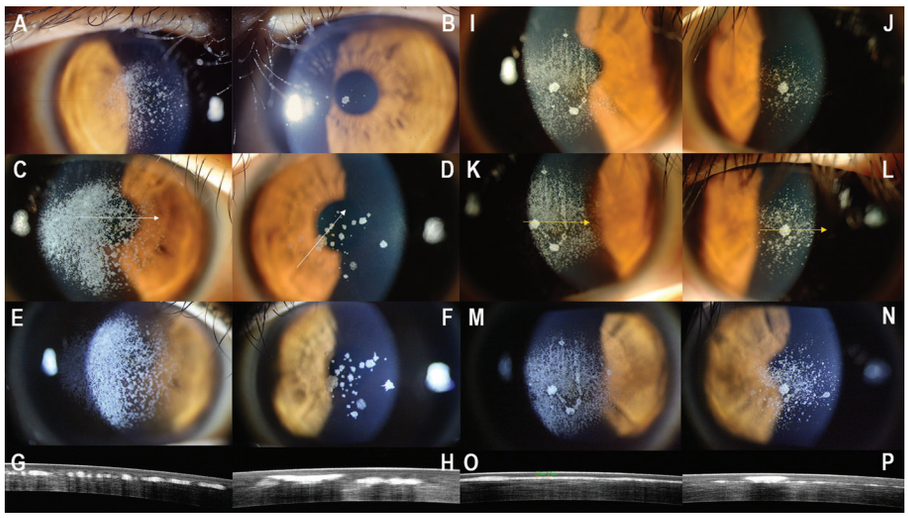

Figure 3 Two heterozygous GCD2 patients (Cases 3 and 4) showing asymmetric exacerbation in both eyes after LASIK A, C, and E: Slit-lamp photographs (Case 3) of the right cornea 1, 7, and 13y after LASIK; B, D, and F: Slit-lamp photographs of the left cornea 1, 7, and 13y after LASIK; G: FD-OCT images show deposits at the stromal interface created by LASIK and were captured along the long white arrow line shown in C; H: FD-OCT images show deposits at the stromal interface created by LASIK and were captured along the long white arrow line shown in D. The progression of corneal deposits was found to be slower in the left eye than the right; I, K, and M: Slit-lamp photographs (Case 4) of the right cornea 3, 4 and 7y after LASIK; J, L, and N: Slit-lamp photographs of the left cornea 3, 4, and 7y after LASIK; O: FD-OCT images show deposits located at the stromal interface created by LASIK and were captured along the long yellow arrow line shown in K; P: FD-OCT images show deposits located at the stromal interface created by LASIK and were captured along the long yellow arrow line shown in L. Both corneas in cases 3 and 4 show ongoing, asymmetric exacerbation. Overall, corneal deposit progression tends to be more severe in LASIK cases compared to SMILE cases. GCD2: Granular corneal dystrophy type 2; LASIK: Laser-assisted *in situ* keratomileusis; FD-OCT: Fourier-domain optical coherence tomography; SMILE: Small incision lenticule extraction.

Japanese researchers have reported a series of cases in which electrolysis was used to remove corneal deposits in patients with Reis-Bücklers corneal dystrophy, recurrent GCD2 after corneal transplantation, and exacerbated GCD2 following LASIK[12]. According to Hieda *et al*[12], electrolysis was performed after flap lift in cases of GCD2 exacerbated after LASIK to treat the deposits on the posterior surface of the flap and the anterior surface of the remaining posterior stroma. The authors reported that the corneal endothelial cell density was 2404 cells/mm^2 in a 66-year-old man, and 2374 cells/mm^2 in a 43-year-old man after electrolysis, and visual recovery was successfully achieved. The follow-up periods, however, were 12 and 6mo, respectively, and longer follow-up would be necessary to evaluate the long-term efficacy of this procedure. If electrolysis were applied to cases of GCD2 exacerbation after SMILE, a potential approach could be to excise the stromal layer anterior to the SMILE-induced interface first, and then to perform electrolysis on the remaining posterior stroma surface, followed by repositioning or amputation of the excised anterior stromal layer. When the corneal stroma anterior to the interface is repositioned, recurrence may occur more rapidly, as suggested by a report of PTK performed after LASIK[7].

In conclusion, to our knowledge, this is the first report of GCD2 exacerbation following bilateral SMILE. This case is particularly notable for its asymmetric progression between the two eyes. In addition to the previously reported case of slowly exacerbated GCD2 after unilateral SMILE, this bilateral case also demonstrated a relatively slow and asymmetric course of exacerbation, providing valuable new insights into the postoperative changes in GCD2 corneal deposits, which appear to be less pronounced after SMILE than after LASIK. Although exacerbation may be delayed following SMILE, its occurrence reinforces that SMILE should be considered contraindicated in patients with GCD2.

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