



Granular corneal dystrophy recurrence at the posterior graft-host interface after type 1 big bubble deep anterior lamellar keratoplasty

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ABSTRACT

Purpose: To describe our observations of granular corneal dystrophy (GCD) recurrence isolated to the posterior graft-host interface after type 1 big bubble (BB) deep anterior lamellar keratoplasty (DALK).

Observations: We performed a retrospective chart review of 3 eyes in 2 patients, and literature review to summarize GCD recurrence patterns after DALK. A 29-year-old man with GCD underwent DALK by type 1 BB technique. Three years following surgery, he was found to have recurrence of GCD deposits isolated to the posterior graft-host interface. Similarly, a 53-year-old woman with GCD underwent DALK by BB type 1 technique, and was noted to have trace residual deposits at the posterior graft-host interface that increased in number and size over the course of 6 years. Her fellow eye underwent DALK with type 2 BB formation, without evidence of graft-host interface recurrence over a four year period. Our literature review describes the recurrence patterns of 18 cases of GCD following DALK.

Conclusions and importance: DALK can be prone to GCD recurrence in the central posterior graft-host interface. Recurrent deposits isolated to the posterior graft-host interface following type 1 BB DALK supports the hypothesis that GCD recurrence may be due to residual pathologic keratocytes in the pre-Descemet layer (PDL).

1. Introduction

Granular corneal dystrophy (GCD) type 1 is an autosomal dominant inherited condition characterized by bilateral grayish-white deposits of hyaline material in the central corneal stroma.¹ The onset of GCD is typically within the first two decades of life, and a progressive increase in the number and size of deposits, and gradual confluence of deposits leads to visual decline. Typically, opacities initially appear in the sub-epithelium, then appear to migrate posteriorly to involve the stroma.¹ When not amenable to superficial treatments, deep anterior lamellar keratoplasty (DALK) has been shown to be effective for visual rehabilitation in GCD, and eliminates the risk of endothelial rejection, compared to penetrating keratoplasty (PKP).² Unfortunately, GCD deposits have been shown to recur within several years following both PKP and lamellar keratoplasty, most often first recurring superficially.³ Both posterior migration of epithelial cell derived hyaline and hyaline production by residual keratocytes have been proposed as potential etiologies of recurrence.³⁻⁶

Interestingly, recurrent hyaline deposits isolated to the posterior graft-host interface have been reported in a few cases to date after non-

Descemet baring DALK,⁵⁻⁷ all with evidence of hyaline in the residual host stroma attached to Descemet membrane (DM). Various techniques for DALK have been developed over the past two decades including manual, hydro-dissection and pneumatic dissection, and vary in the amount of stroma removed.⁸ The big bubble (BB) technique was initially described by Anwar and Teichmann in 2002, and is thought to leave behind the least amount of residual stroma, cleaving a plane between a “pre-Descemet layer” (PDL) (Type 1 BB), the DM itself (Type 2 BB) and the rest of the stroma, or a mixed plane partially exposing both PDL and DM (Type 3 BB).⁸⁻¹²

Here we present two cases of recurrent GCD deposits following type 1 BB DALK isolated to the posterior graft-host interface, and the fellow eye of one case without interface recurrence at four years after a type 2 BB was formed during DALK. We have also reviewed all reported cases of GCD recurrence after DALK, and have summarized the timing and recurrence patterns for comparison. Our observations further suggest the importance of considering the risk of leaving any residual central host stromal tissue behind in the surgical treatment of GCD because residual host keratocytes within the PDL could be an important source of recurrent hyaline deposition.

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2. Methods

A retrospective chart review was performed of 3 eyes of 2 patients who underwent DALK and presented with recurrent GCD deposits in the posterior graft-host interface.

The PubMed library was searched electronically for peer-reviewed literature in April 2019 without date restrictions. Key words used in the search included “granular”, “dystrophy”, “recurrence”, “Groenouw”, and “Avellino”. Inclusion criteria were defined as original studies describing recurrence of GCD after DALK. There were no restrictions on publication date or study design. Studies were screened for the following exclusion criteria: (1) not written in English, (2) not fully accessible online. The titles of 104 articles were reviewed of which 60 were found to be pertinent to the research. The abstracts were read and evaluated, and 11 articles were read in their entirety. Ultimately, 8 studies were included according to their relevance to the subject.

3. Results

3.1. Case 1

A 29-year-old Hispanic man was referred for one year of progressively worsening vision in both eyes. The best-corrected visual acuity (BCVA) at initial evaluation was 20/50 in the right eye and 20/30 in the left eye. A slit lamp examination was notable for bilateral snowflake-like opacities in the central anterior stroma with a clear zone peripherally. Anterior segment optical coherence tomography (OCT) revealed opacities extending to the mid and posterior stroma (Fig. 1). The patient was significantly bothered by the vision in his right eye and elected to proceed with DALK.

An 8.25 mm trephine was used to partially cut the host corneal tissue. A small paracentesis was made temporally, and a gas bubble injected into the anterior chamber. An angled beaver blade was used to dissect and remove the anterior cap of stroma. A 30-gauge needle was used to create passage for 27-gauge Fogla cannula into the posterior stromal space, through which air was forcefully injected. A type 1 BB was created. Viscoelastic was placed on the central stroma, a blade was used to enter the BB, and additional viscoelastic was used to fill the cleavage plane. Tan DALK scissors were used to excise the stromal tissue. An 8.50 mm trephine was used to prepare the donor tissue, from which the endothelium and DM were removed. The graft was sutured in place using a total of 16 interrupted 10–0 nylon sutures.

Histological examination of the host cornea specimen showed stromal deposits highlighted with Masson Trichrome stain and negative for Congo Red stain, consistent with GCD type I. Over the next two years, the patient had sutures removed with some residual irregular astigmatism. With a scleral lens, the patient’s BCVA was 20/25 + 2. Three years following the surgery, he complained of decreased vision in his right eye. His BCVA was 20/30-. The exam was notable for diffuse corneal opacities at the posterior graft-host interface (Fig. 2A), with new hyper-reflective lesions visible by anterior segment OCT (Fig. 3A). The patient was not interested in any additional intervention at that time and was lost to follow-up after the visit three years following surgery.

3.2. Case 2

A 53-year-old Hispanic woman initially presented with decreased vision in both eyes. Her BCVA was 20/100 + 1 in the right eye and 20/

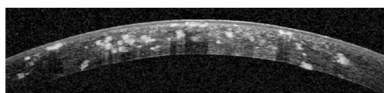


Fig. 1. Anterior segment OCT of case 1 on initial presentation, with scattered opacities throughout the stroma.

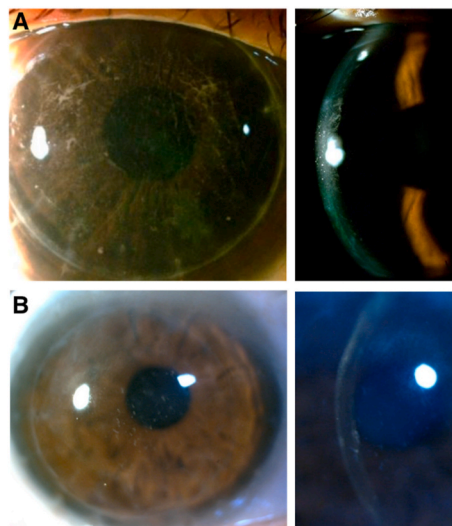


Fig. 2. Slit lamp photographs. (A) Case 1: 3 years following DALK with Type 1 BB in right eye, (B) Case 2: 6 years after DALK with Type 1 BB in right eye. An optical cross-section of the cornea shows diffuse white opacities at the graft-host interface (A and B).

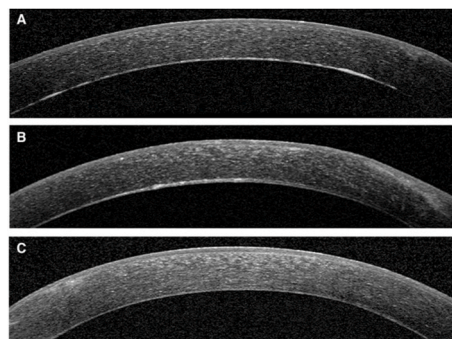


Fig. 3. Anterior segment OCT. (A) Case 1 right eye 3 years after Type 1 BB DALK, (B) Case 2 right eye: 6 years after Type 1 BB DALK, and (C) Case 2 left eye: 4 years after Type 2 BB DALK. Hyper-reflective lesions are seen densely packed along the graft-host interface, and correspond to the deposits in Fig. 2A and B.

60–1 in the left eye. A slit lamp exam showed discrete white central stromal deposits with clear intervening spaces in both eyes, consistent with GCD. The patient was significantly bothered by the decline in vision in her right eye, and elected for surgical intervention. She underwent a similar type 1 BB DALK procedure as described in the first case. Histological examination of the host corneal specimen showed Masson Trichrome positive and Congo Red negative stromal deposits, also consistent with GCD type 1. One day following surgery, the patient was noted to have trace scattered opacities at the level of the graft-host interface consistent with persistent GCD deposits within the PDL. Sutures were removed over the next 3 years, and the BCVA improved to 20/25 in the right eye with a contact lens. Six years after DALK, her BCVA decreased to 20/40 in the right eye, and slit lamp examination and OCT of the right eye showed an interval increase in size and number of deposits at the graft-host interface (Figs. 2B and 3B). She was also noted to have mildly increased nuclear sclerosis of her lens.

The patient also underwent DALK for similarly visually significant GCD in the left eye three years following the right eye surgery, at the age of 56. In this case, formation of a type 2 BB was noted. The case was complicated by intra-operative peripheral DM rupture, but the DM became successfully reattached after tamponade with intracameral air. Again, the diagnosis of GCD type 1 was confirmed by the presence of

Masson Trichrome-positive and Congo Red negative staining of stromal deposits in the excised host cornea. The post-operative course was complicated by partial stromal rejection after the patient ceased using prednisolone acetate 1% one month after surgery, but this improved after the patient resumed the prescribed steroid regimen. After all the sutures were removed, she underwent subsequent cataract surgery. Four years after type 2 BB DALK in the left eye, her BCVA was 20/30, and there has been no evidence of GCD recurrence in the posterior graft-host interface (Fig. 3C).

3.3. Literature review

We found 18 reported cases of GCD recurrence after DALK in the literature, summarized in Table 1. The timing of recurrence ranged from 6 months to 8.5 years. The patterns of recurrence were varied. There were three cases of confirmed posterior graft-host interface recurrence, and up to three others where this recurrence pattern was mentioned, but not shown. Up to eight cases involved the epithelium, sub-epithelium or anterior stroma. Up to nine cases involved the vertical graft-host junction area, suture tracts or arcuate incision sites.

Table 1

Summary of time to recurrence and location of deposits for 18 cases of granular corneal dystrophy following deep anterior lamellar keratoplasty reported in the literature.

Case Series	N	Surgical technique	Mean time to documented recurrence (range)	Location of deposits
Lewis et al. (2017) ⁷	4	Anwar big bubble and manual dissection	1.2 years	Central basal epithelium and anterior stroma (N = 3). Posterior graft-host interface (manual dissection N = 1)
Avadhanam et al. (2016) ¹⁵	3	Unspecified	5.4 (3–8.5) years	Preferentially in graft-host interface and along suture tracts and arcuate incisions (Posterior graft-host interface pattern not explicitly shown)
Scorcia et al. (2015) ¹⁹	1	Big bubble	48 months	Unspecified; presumably, within DALK donor tissue that was replaced with DALK graft exchange
Pantaneli et al. (2014) ⁵	1	Melles manual dissection	3 years	Host stroma anterior to Descemet membrane
Rama et al. (2013) ⁶	1	Unspecified	6 months	Posterior graft-host interface
Unal et al. (2013) ²	2	Anwar big bubble or manual dissection	14 months (N = 1)	Unspecified
Salouti et al. (2009) ¹⁴	5	Melles manual dissection	15.6 ± 1.8 (13–16) months	Early – along suture tracts and peripheral graft-host junction. Late – superficial subepithelial area, peripheral stroma extending centrally
Park et al. (2007) ²⁰	1	Unspecified	13 months	Periphery adjacent to the graft-host junction

N = number of documented recurrence events.

4. Discussion

These cases illustrate that GCD can recur in the posterior graft-host interface even after type 1 BB DALK, and are to our knowledge the first report of isolated recurrence within the PDL after type 1 BB DALK. A few prior cases have been reported of DALK posterior graft-host interface GCD recurrence, but in these cases manual lamellar dissection was performed,^{5,7} or likely to have been performed,⁶ leaving behind more posterior stromal tissue and associated keratocytes. Similar to our case #2, Muller et al. found that residual GCD deposits could be seen in the PDL after type 1 BB formation.¹³ However, the fact that these deposits increased in number in our second case illustrates that there are likely residual keratocytes that continue to produce keratoepithelin in the remaining host tissue posterior to the type 1 BB cleavage plane.

GCD deposits commonly recur within a few years after corneal transplantation, whether by DALK or PKP.³ Various patterns of GCD recurrence following DALK and PKP have been reported. The most common initial site seems to be the sub-epithelial region (Table 1), suggesting that host epithelial cells are an important source of the hyaline deposits, which explains why the deposits can occur in grafted tissue. For instance, Lyons et al. found that early recurrences developed in the sub-epithelium, adopting a vortex pattern, with subsequent progression into the posterior stroma.³ Almost all patients had recurrence by 36 months after surgery. Frising et al. described similar cases of superficial GCD recurrence, suggesting an epithelial origin, as well as a case in which deeper stromal deposits were found in previous suture tracts, suggesting a mechanism whereby surgical incisions may act to facilitate the migration of epithelial deposits.⁴ Several other case reports have also demonstrated recurrent superficial deposits localized to the peripheral stroma, extending centrally, often with involvement of suture tracts and vertical incision lines.^{14,15}

However, the cases presented in this report and the others mentioned above of isolated posterior graft-host interface GCD recurrent suggest that keratocytes can also be an important source of hyaline deposits in GCD. Epithelial migration seems an unlikely explanation in these and in our cases, when recurrence does not initially develop in the vertical graft host junction with clear migration from the peripheral to central posterior interface. In our review of reported GCD recurrence patterns after DALK, about half of the cases involved superficial recurrences or recurrences around suture tracts, suggesting an epithelial source, and up to one third involved isolated posterior graft-host interface recurrence suggesting a keratocyte source (Table 1).

Furthermore trauma to stromal tissue during BB formation in DALK could be leading to activation of keratocytes and subsequent deposition of hyaline in the cleavage plane, such as in GCD type 2 exacerbation after LASIK.¹⁶ GCD type 2 is genetically distinct from GCD type 1, and leads to both hyaline and amyloid deposition, but it is hyaline that has been detected in these cases of laser-induced deposits occurring within LASIK flap interfaces.^{1,16,17} Thus, there may be some similarity between the mechanisms of recurrence or exacerbation in type 1 GCD after DALK and type 2 GCD after LASIK. Hyaline deposit formation may be triggered by tissue trauma resulting in host keratocyte hyaline production. Trauma to keratocytes may also explain the recurrence patterns noted around suture tracts and vertical incisions, and may also explain why posterior DALK interface recurrence was observed as early as 6 months by Rama et al.⁶

The clinical significance of our observed recurrence pattern is that deep central deposits are not amenable to less invasive therapies, and generally PKP would become necessary. Interestingly, there has not been a similar early recurrence at the DALK interface in our second patient's left eye after type 2 BB DALK at the four-year mark. This is not to say that recurrence will not happen after type 2 BB DALK. It most certainly will, but perhaps removal of the host PDL potentially avoids early deep central recurrence of GCD, which is more of a challenge to manage than superficial or peripheral recurrences. Despite this hypothesis, even if it were possible to control, we would not advocate for

the purposeful creation of a type 2 BB as they are prone to intra-operative perforation, as was the case in our patient. Rather, our cases illustrate that using the most superficial form of treatment possible to achieve a satisfactory visual outcome is advisable. DALK should perhaps be reserved in cases of extensive deep posterior opacities. Moreover, the risk of isolated deep recurrence with DALK, may be one reason to consider PKP over DALK, despite the lower rejection rate with DALK.¹⁸ However, a better understanding of the frequency of deep interface recurrence after DALK is needed to be able to guide this decision.

A limitation of our report is that we were not able to obtain genetic testing in our cases, and thus cannot be absolutely certain as to whether these patients had GCD type 1 or 2; however, clinical and histological examination pointed to a diagnosis of GCD type 1. Nevertheless, it would be interesting to determine in future studies whether genetic differences influence the risk of early deep stromal DALK interface recurrence in GCD. Finally, our report consists of two retrospectively reviewed cases, and we believe further investigation to quantify and directly compare recurrence between PKP and DALK may help better guide surgical planning in GCD.

Patient consent

Written informed consent was obtained from one of the patients. The other patient was lost to follow-up, and consent could not be obtained. The study is in accordance with HIPPA regulations. This report does not contain any personal information that could lead to the identification of the patients.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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