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Corneal Guttae After Descemet Membrane Endothelial Keratoplasty

Keamela Vasanthananthan, MD,† Vincent J. A. Bourgonje, PhD,*† Jessica T. Lie, PhD,*‡ Rana Mulders-Al-Saady, MD,*† Esther A. Groeneveld-van Beek, MSc,*‡ Jacky de Leeuw, BSc,* Alina Miron, MSc,* Robert H. J. Wijdh, MD,§ Remco Stoutenbeek, MD, PhD,§ Gerrit R. J. Melles, MD, PhD,*†‡ Silke Oellerich, PhD,* and Viridiana Kocaba, MD, PhD*†‡¶*

Purpose: The aim of this study was to report on the occurrence of corneal guttae after Descemet membrane endothelial keratoplasty (DMEK).

Methods: In this retrospective case series, 13 eyes of 13 patients who underwent DMEK at 2 tertiary referral centers between 2007 and 2021 (average available follow-up 73 ± 52 months, range 18–174 months) and showed corneal guttae during postoperative examinations were included. Eye bank images were retrospectively reviewed.

Results: Occurrence of guttae was observed by specular microscopy in 13 eyes. In 11 cases, presence of guttae was confirmed by confocal microscopy and in 1 case by histology. Five eyes showed an increase in guttae density during the postoperative course. Surgery indications were Fuchs endothelial corneal dystrophy (n = 11), pseudophakic bullous keratopathy (n = 1), and DMEK graft failure after allograft rejection (n = 1); the latter eye had shown no signs of guttae after primary DMEK. Two eyes with guttae required a repeat DMEK due to graft failure. At the last available follow-up, all 11 remaining eyes had clear corneas and 10 eyes had a best-corrected visual acuity of ≥0.9 (decimal). During donor cornea processing in the eye bank, no guttae were observed on the donor tissue.

Conclusions: Corneal guttae can occur after DMEK including in eyes operated for indications other than Fuchs endothelial corneal dystrophy and most likely guttae were present on the donor graft but were not detectable by routine slit-lamp and light microscopy evaluation in the eye bank. Postoperative guttae density varies among patients and especially small isolated guttae do not seem to affect clinical outcomes.

Key Words: Fuchs endothelial corneal dystrophy, DMEK, endothelium, guttae, eye banking

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Fuchs endothelial corneal dystrophy (FECD) is the most common corneal endothelial dystrophy and is the primary indication for corneal transplantation worldwide.[1,2] The disease is characterized by morphological and physiological alterations in the endothelium and formation of guttae, hallmark of FECD, leading to continuous and gradual loss of endothelial cells with subsequent development of corneal edema in advanced stages of the disease.[1,3] The prevalence of corneal guttae in a White population was found to be 9% to 11% in women and 4% to 7% in men.[4,5] Screening of corneal donor tissue for the presence of guttae by light microscopy or specular microscopy is part of routine eye bank protocol.[6] The detection of guttae, however, can be challenging, and the occurrence of guttae after corneal transplantation has been reported.[6–15] Isolated corneal guttae or patches of confluent corneal guttae have been identified in up to 25% of corneal grafts after penetrating keratoplasty[6] and in up to 18.7% of corneal grafts after Descemet membrane endothelial keratoplasty (DMEK).[14] Because DMEK is nowadays a preferred treatment option for endothelial diseases, in the current study, we report in more detail on the different appearances of corneal guttae after DMEK and on the longer-term effect of the guttae on clinical outcomes.

MATERIALS AND METHODS

Patient Data

In this retrospective case series, 13 eyes of 13 patients who were operated at 2 tertiary referral centers between 2007 and 2021 and showed suspected guttae during routine specular microscopy examinations were included. The mean patient age was 62 ± 12 years, 5 patients were female and 8 were male. Six patients were phakic and 7 patients were pseudophakic (Table 1). All patients provided written informed consent before surgery for research participation and the study adhered to the Declaration of Helsinki. Because

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From the *Netherlands Institute for Innovative Ocular Surgery, Rotterdam, the Netherlands; †Melles Cornea Clinic Rotterdam, Rotterdam, the Netherlands; ‡Amnitrans EyeBank Rotterdam, Rotterdam, the Netherlands; §Universitair Medisch Centrum Groningen, Groningen, the Netherlands; and ¶Tissue Engineering and Cell Therapy Group, Singapore Eye Research Institute, Singapore

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Correspondence: Viridiana Kocaba, MD, PhD, Netherlands Institute for Innovative Ocular Surgery, Laan op Zuid 88, 3071AA Rotterdam, the Netherlands (e-mail: viridiana_k@yahoo.fr).

of the retrospective nature of the research, institutional review board approval was not required.

DMEK Graft Preparation and Surgery

Thirteen DMEK grafts of 11 donors were prepared at Amnitrans EyeBank Rotterdam, The Netherlands. At the arrival in the eye bank, donor corneas were initially screened using a slit-lamp microscope. DMEK grafts were prepared using hydrodissection and/or no-touch techniques as previously described.[16,17] DMEK grafts were stained with hypotonic trypan blue 0.04% solution (Hippocratech, Rotterdam, the Netherlands), then evaluated, and photographed with up to 200× magnification with an AxioVert.A1 microscope (Zeiss, Oberkochen, Germany). Endothelial cell density (ECD) of the DMEK grafts was assessed in the eye bank using the fixed-frame method determined by averaging the counts performed manually on 3 fixed frames of 0.01 mm^2 per graft.[17] Grafts were considered eligible for transplantation if ECD was ≥2300 cells/mm^2, outcome of central and peripheral visual inspection after graft preparation was unremarkable (ie, absence of Descemet membrane tear, absence of bare Descemet membrane areas, abnormal endothelial cell morphology, and presence of guttae), and microbiological testing was negative. DMEK grafts were then stored free-floating in organ-culture medium

TABLE 1. Patient and Donor Characteristics

Patient/Donor Data							
Case #/Center	**OD/OS**	**Indication**	**Lens Status**	**Patient Sex (F/M)**	**Patient Age (y)**	**Donor Sex (F/M)†**	**Donor Age (y)†**	**Last Avail. FU (m)**
1/1	OD	FECD	Phakic	M	39	F	69	174
2/1	OS	FECD	Pseudophakic	F	74	M	50	162
3/1	OS	Failed DMEK	Pseudophakic	M	65	M	65	108
4/1	OD	PBK	Pseudophakic	F	56	M	65	108
5/1	OD	FECD	Phakic	M	55	M	69	72
6/1	OS	FECD	Phakic	M	59	M	61	72
7/1	OD	FECD	Phakic	F	55	M	61	54
8/1	OD	FECD	Phakic	F	46	M	65	18
9/1	OS	FECD	Pseudophakic	F	74	M	77	60
10/1	OD	FECD	Phakic	M	64	M	70	60
11/1	OS	FECD	Pseudophakic	M	75	M	84	24
12/2	OD	FECD	Pseudophakic	M	79	M	73	18
13/2	OD	FECD	Pseudophakic	M	70	M	73	20

Patient/Donor Data	BCVA (Decimal)				CCT (μm)				ECD (Cells/mm^2)*					
Case #/Center	**Preop**	**6m FU**	**12m FU**	**At Last Avail. FU**	**Preop**	**6m FU**	**12m FU**	**At Last Avail. FU**	**Preop. donor**	**6m FU**	**12m FU**	**At Last Avail. FU**	**Guttae First seen**	**Remarks**
1/1	0.4	n.a.	n.a.	1.0	n.a.	n.a.	n.a.	533	2640	n.a.	n.a.	1356	8 y‡	
2/1	0.4	1.0	1.0	0.95	618	493	493	493	2750	610	550	631	1 m	
3/1	0.2	0.5	0.2	0.35	757	544	549	555	2600	960	625	683	1 m	Rebubbling 1m postop.; PPV + ERM peeling at 11 m postop.
4/1	0.05	1.0	0.8	0.95	1060	502	527	598	2400	1282	1270	936	1 m	
5/1	0.6	0.9	0.9	0.5	653	497	508	654	2500	535	571	625	1 wk	Re-DMEK at 74 m postop.
6/1	0.7	1.0	0.8	1.0	617	468	485	528	2600	873	790	757	2 wk	Rebubbling 2 wks postop.
7/1	0.5	0.9	0.9	0.16	655	525	524	692	2500	1046	889	510	1 m	Re-DMEK at 56 m postop.
8/1	0.3	n.a.	n.a.	1.0	568	n.a.	n.a.	516	2400	n.a.	n.a..	n.p.	1 wk	
9/1	0.5	0.8	1.0	1.0	690	528	524	547	2700	1513	1671	908	1 wk	
10/1	0.6	1.0	0.9	0.9	662	523	523	525	2900	1789	1743	1510	1 wk	
11/1	0.5	n.a.	1.0	1.2	783	n.a.	485	497	2700	n.a.	1543	1671	1 wk	
12/2	0.5	n.a.	n.a.	0.9	615	n.a.	n.a.	565	2400	n.a.	n.a.	n.a.	3 m	No confocal scans available
13/2	0.8	n.a.	n.a.	0.9	637	n.a.	n.a.	495	2500	n.a.	n.a.	n.a.	3 m	

Centers: 1 = Melles Cornea Clinic Rotterdam and 2 = University Medical Center Groningen.

*Endothelial cell density values are only indicative because depending on guttae density, only small areas without guttae could be used for the cell counting and these areas may not be representative for the entire graft.

†Contralateral donor corneas: DMEK grafts originated from the same donor for study no. 6 and 7, and 12 and 13, respectively.

‡Patient returned for first postoperative check-up 8 years after DMEK; previous check-ups were performed at a different center abroad.

Avail., available; BCVA, best-corrected visual acuity; CCT, central corneal thickness; ERM, epiretinal membrane; FECD, Fuchs endothelial corneal dystrophy; F/M, female/male; m, months; n.a., not available; n.p., not possible; OD/OS, right/left eye; PBK, pseudophakic bullous keratopathy; postop., postoperatively; PPV, pars plana vitrectomy; preop., preoperative; re-DMEK, repeat Descemet membrane endothelial keratoplasty; wks, weeks; y, years.

(CorneaMax; Eurobio, Courtaboeuf, France) until the transplantation. The mean donor age was 68 ± 8 years, the sex ratio was 10 men for 1 women, and the mean donor ECD after preparation was 2585 ± 153 cells/mm^2 (Table 1). All DMEK surgeries were uneventful and performed as a single procedure based on the standardized "no-touch" technique.[18]

Postoperative medication included topical chloramphenicol 0.5% 6 times daily during the first postoperative week, and 2 times daily during the second week, and ketorolac tromethamine 0.4% and topical dexamethasone 0.1% 4 times daily for 4 weeks. After 1 month, the medication was switched to fluorometholone 0.1% 4 times daily, followed by a routine tapering regimen. After 1 year, the patients were advised to continue the use of fluorometholone 0.1% once per day or every other day for an indefinite period.

Data Collection

Patient outcome data were collected from preoperative and routine follow-up visits. During these consultations, examinations included best-corrected visual acuity assessment, Scheimpflug imaging (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany), specular microscopy (Topcon Medical Europe BV, Capelle a/d IJssel, the Netherlands), and slit-lamp biomicroscopy. In case suspected guttae were observed during the routine specular microscopy examination, in vivo confocal microscopy (IVCM, HRT3 Rostock cornea module, Heidelberg Engineering GmbH, Heidelberg, Germany) was performed. Postoperative ECD was evaluated using a noncontact specular microscope (Topcon SP3000, Topcon Medical Europe BV). ECD assessments were performed using the commercial software of the specular microscope (ImageNet software, Topcon Medical Europe). The automatic cell border recognition program was used to provide ECD analysis. The automatically delineated cell borders were checked and manually reassigned by a trained technician in case of incorrect assignment. For each follow-up, 3 to 5 images were taken centrally and 1 to 3 images were taken pericentrally. The results of 3 central ECD measurements were averaged. In case of the presence of guttae, the specular microscopy images were analyzed based on central guttae using 3 to 5 images per patients and follow-up time point and categorized into 2 groups: ≤10 guttae per image or >10 guttae per image.

Two DMEK grafts with suspected guttae that were removed during repeat DMEK procedures were analyzed by light microscopy (Axio Vert.A1, Zeiss, Oberkochen, Germany) and then fixated in formalin and processed for histology. Paraffin-embedded sections were cut with a microtome (Thermo Scientific, Breda, The Netherlands) and stained with hematoxylin-eosin (HE) and periodic acid–Schiff (PAS). Light microscopy images taken at the eye bank during tissue processing were retrospectively reviewed for the donor corneas of the affected DMEK grafts.

RESULTS

Occurrence of guttae after DMEK was observed during routine postoperative specular microscopy examination in 13 eyes of 13 patients with average available follow-up of 73 ± 52 months (median 60 months; range 18–174 months). Presence of guttae was confirmed by IVCM (n = 11) or histology (n = 1). For 1 case (case #12), IVCM examination was not available but slit-lamp biomicroscopy showed the presence of central guttae (see Figure, Supplemental Digital Content 1, http://links.lww.com/ICO/B534). None of the eyes showed any Descemet membrane remnants as a result of an incomplete descemetorhexis.

Surgery indications of eyes with occurrence of guttae after DMEK were FECD (n = 11) (Figs. 1,2), pseudophakic

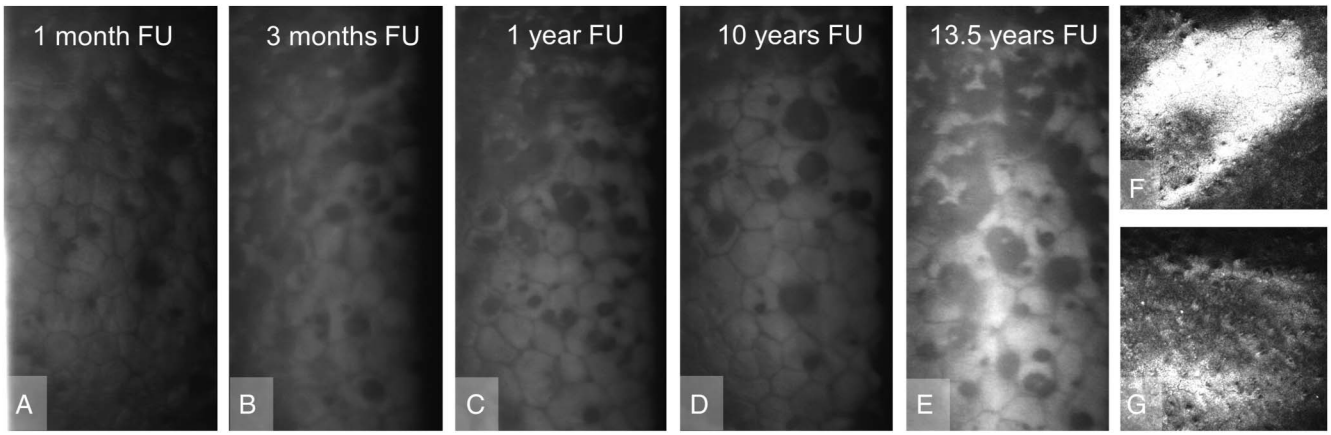

FIGURE 1. Specular microscopy and in vivo confocal microscopy images of case #2 after DMEK. A–E, Central specular microscopy images of case #2 who underwent primary DMEK for Fuchs endothelial corneal dystrophy. Images show corneal guttae as early as (A) 1 month postoperatively. The density of guttae seems to remain relatively constant throughout the follow-up period up to (E) 13.5 years, but the size of the guttae seems to increase over time. This, however, can also be an imaging artifact as the size of the guttae on the specular microscopy images depend on the focal plane of the images (see Figure, Supplemental Digital Content 2, http://links.lww.com/ICO/B535). In reference 19, the eye shown here was described as having "superimposed dark spots" rather than corneal guttae[19]; however, in vivo confocal microscopy at the 13.5-year follow-up (F, G) confirmed the presence of corneal guttae.

bullous keratopathy (n = 1) (Fig. 3), and DMEK graft failure after allograft rejection (n = 1) (Table 1). The latter eye underwent repeat DMEK 56 months after primary DMEK and had shown no signs of guttae after primary DMEK. Nine patients with FECD had undergone bilateral DMEK and 6 of these patients had specular microscopy images available of the contralateral eyes, which showed no occurrence of guttae.

Occurrence of guttae was observed within the first postoperative month in 10 of 13 cases. Two other cases (#12 and #13) had the first specular microscopy images taken at the 3-month follow-up, which showed the presence of guttae, and another case (#1) was a patient from abroad who returned for the first follow-up at 8 years after DMEK (Table 1). Of the 10 patients (#2–11) who had specular microscopy images available from within the first postoperative month to the last available follow-up, 8 showed less than 10 guttae per central specular microscopy image at the 1-month follow-up (cases #3–10) and 2 had more than 10 guttae (cases #2 and #11). For the latter 2 eyes, the density of guttae seemed to remain stable over time, whereas it increased for 5 eyes with initially less

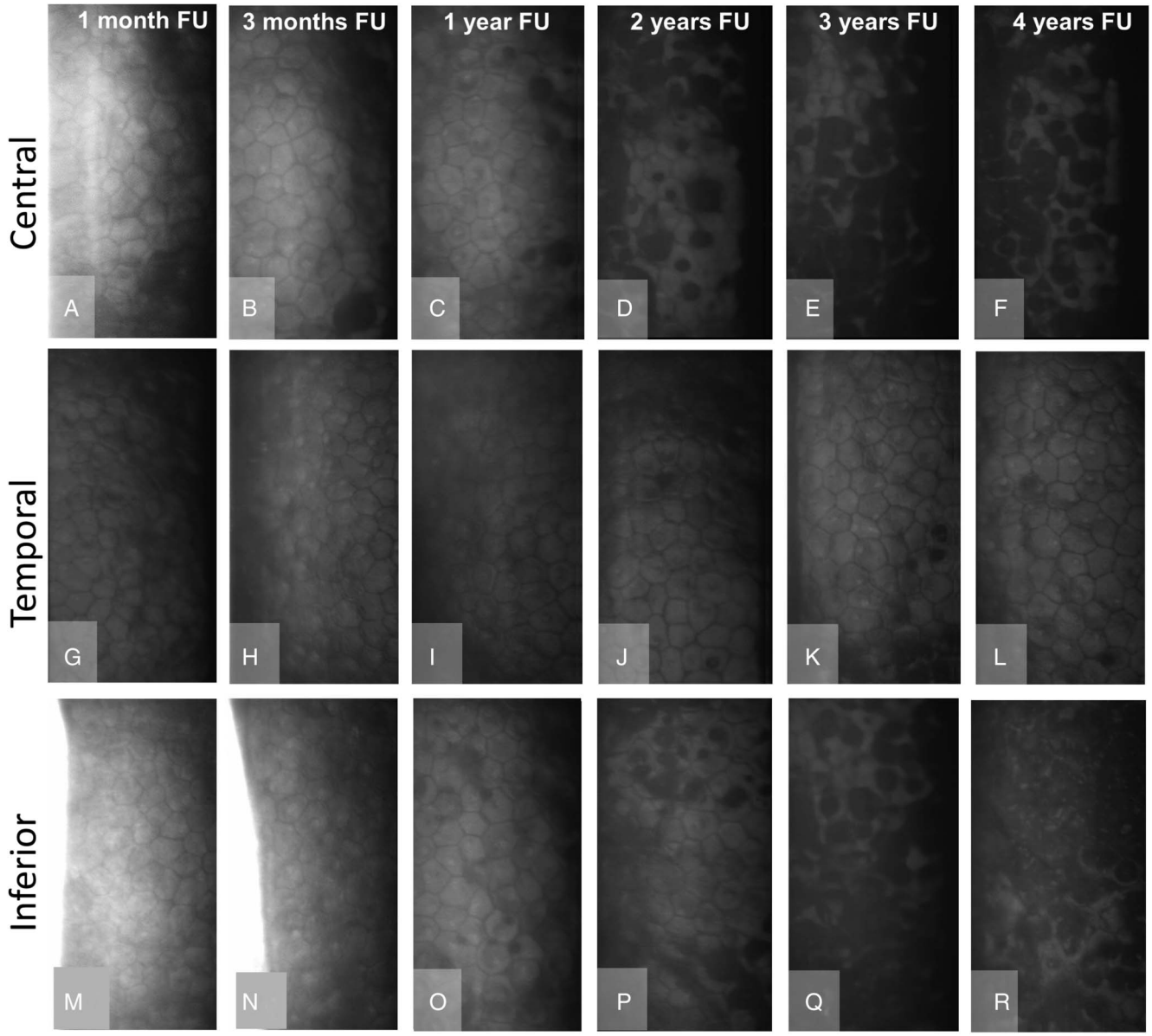

FIGURE 2. Central and paracentral specular microscopy images of case # 5 after DMEK. Specular microscopy images of case #5 of the (A–F) central, (G–L) temporal, and (M–R) inferior regions taken at different follow-up visits. Central specular microscopy images show a low density of corneal guttae at the (A) 1 month and (B) 3 months follow-up. From the (C) 1-year follow-up onward, the density of guttae increases until almost the entire surface depicted in the images (E, F) is covered by guttae. Although the density of guttae increases centrally, the same changes are not observed in the specular microscopy images taken in the (G–L) temporal area (approximately 2.5 mm from the corneal center), while the (M–R) inferior region shows similar changes as the corneal center. The patient underwent repeat DMEK surgery at 74 months postoperatively.

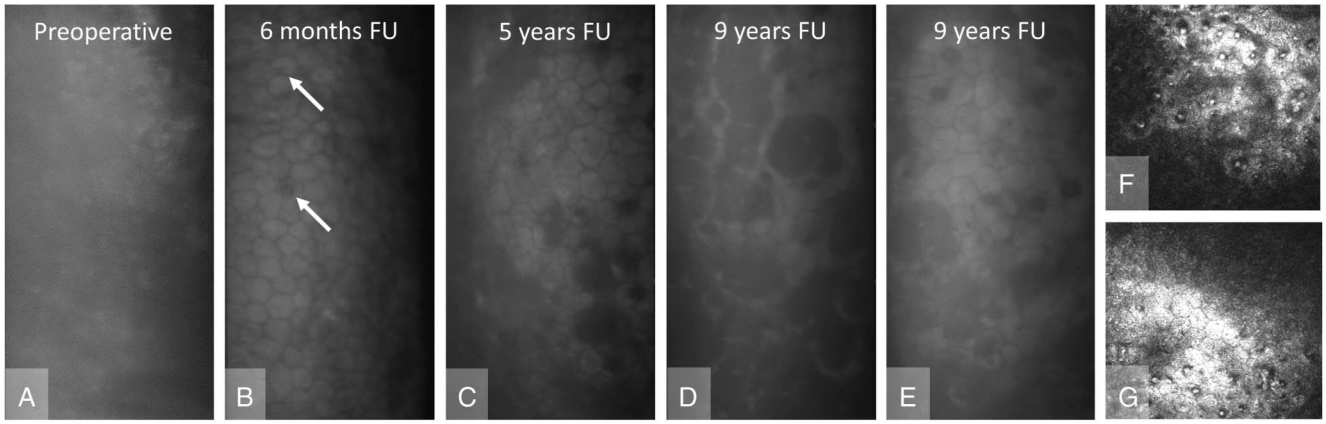

FIGURE 3. Specular microscopy and in vivo confocal microscopy images of case #4 after DMEK. A–E, Central specular microscopy images of case #4 who underwent primary DMEK for pseudophakic bullous keratopathy. A, Specular microscopy image taken preoperatively was blurred because of corneal edema but still showed residual corneal endothelial cells. B, Postoperatively, only small isolated guttae were visible within the first postoperative months (white arrows), but the guttae density increased (C, D, E) at 5 and 9 years postoperatively. Images (D, E) were both taken at the 9-year follow-up in the central area and differed distinctively in the density and size of the observed guttae, which may be due to differences in the focal image plane and/or inhomogeneous guttae distribution within the central area (assuming that not exactly the same 0.25 mm × 0.5 mm area was covered by the 2 images). F, G, Presence of corneal guttae was confirmed at the 9-year follow-up by in vivo confocal microscopy and similar to the specular microscopy images (F, G), the confocal images also show differences in guttae density.

than 10 guttae. Distribution of guttae in the center of the cornea was, however, not homogeneous and could show distinct variations between specular images (Figs. 3D, E) and IVCM images (Figs. 3F, G), respectively, that were taken at the same follow-up and within the central area of the cornea. In addition, appearance of guttae in specular microscopy images also depends on the focal plane of the image (see Figure, Supplemental Digital Content 2, http://links.lww.com/ICO/B535). Guttae appear larger and more pronounced when the image was focused on the guttae, whereas they appear as blurry shades when the image is focus on the endothelial cell layer.

Guttae distribution differed between central and paracentral regions. In 2 eyes (cases #9 and #11), guttae were only observed centrally and in the other eyes also paracentrally. Distribution between different paracentral regions could vary distinctively (Fig. 2) and guttae density could also be higher paracentrally than centrally (Fig. 4).

Two patients (cases #5 and 7, Table 1) required a repeat DMEK procedure at 56 and 74 months postoperatively, respectively, for secondary graft failure. Case #5 showed centrally a substantial increase in guttae density after the first postoperative year (Fig. 2). Guttae density on the specular microscopy images taken centrally remained low for case #7 throughout the follow-up period; however, light microscopy and histology analysis of the removed DMEK graft clearly indicated the presence of guttae on the graft (Fig. 5).

At the last available follow-up, the corneas of the 11 remaining eyes were clear and all patients, except for case #6, were without complaints. Best-corrected visual acuity at the last available follow-up was ≥0.9 (decimal) for 10 of the 11 remaining patients. All details of the clinical outcomes are listed in Table 1.

Donor tissue had been screened in the eye bank before graft preparation with slit-lamp and light microscopy evaluation according to the local eye bank protocol (see Figure, Supplemental Digital Content 3, http://links.lww.com/ICO/B536). No guttae had been noted during donor cornea processing in the eye bank. The 13 DMEK grafts included 2 graft pairs (cases #6 and 7, cases #12 and 13) originating from the same donors. Of the contralateral tissues of the other 9 donors, 2 corneas were not used for transplantation and the other corneas were transplanted at other centers, but no verifiable follow-up information was available for these grafts.

DISCUSSION

This case series describes the occurrence of corneal guttae after DMEK transplantation and shows that there is a high variability in guttae density, appearance, location, and progression among patients. The prevalence of corneal guttae in a White population of 50 years or older was reported to be 9.2% in the Reykjavik Eye Study with a higher prevalence in women than in men.[5] The widespread presence of corneal guttae in the elder population should have a direct impact on corneal eye banking as a similar percentage of donor corneas should be expected to contain corneal guttae. Borderie et al reported that even 26% of donor corneas showed either few, scattered guttae (21%) or clusters of guttae (5%),[6] while our eye bank discards on average about 10% of donor corneas due to corneal guttae (unpublished results). Screening for corneal guttae is part of the standard eye bank protocol, but corneal guttae can be challenging to identify by light microscopy because they might, for example, still be covered by endothelial cells. This may result in donor tissue containing guttae being released for transplantation and guttae becoming visible postoperatively.[6–15] Reported incidences of postoperative corneal guttae varies in the literature for penetrating and endothelial keratoplasty. For penetrating

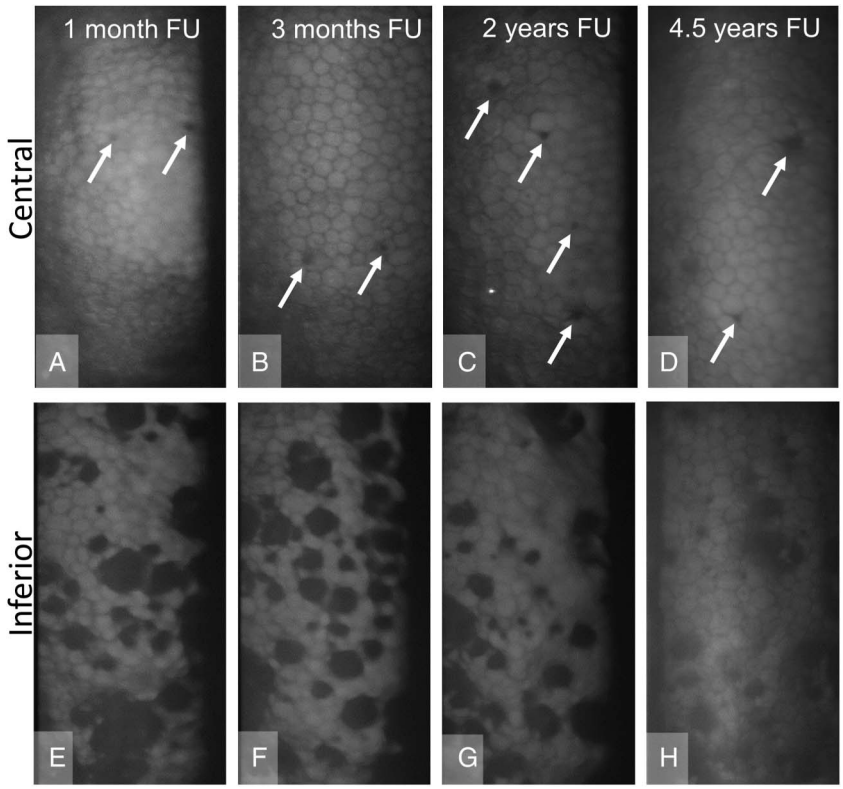

FIGURE 4. Central and paracentral specular microscopy images of case #10 after DMEK. A–D, Central and (E–H) inferior specular microscopy images of case #10 who underwent primary DMEK for Fuchs endothelial corneal dystrophy. A–D, Central specular microscopy images show only small isolated corneal guttae throughout the follow-up period of 4.5 years, whereas (E–H) images taken in the paracentral inferior area (approximately 2.5 mm from the corneal center) show a high density of larger corneal guttae from the first postoperative month (E) onward.

keratoplasty (PK), corneal guttae were observed in 13% to 26% of the grafts,[6,10,15] for Descemet stripping automated endothelial keratoplasty (DSAEK) in 3% of the grafts (from the same study that reported a rate of 13% after PK),[6] and for DMEK in 4% to19% of the eyes.[11,14]

Occurrence of corneal guttae in this case series could be detected within the first postoperative month which corroborates previous reports on the early guttae occurrence after DSAEK and DMEK.[9,11] Along with the fact that corneal guttae have been observed for patients with surgery indications other than FECD,[6–10,12,15] this supports the hypothesis that the corneal guttae originate from the donor tissue. Differences in the reported postoperative incidence of corneal guttae could then either be due to differences in the screening protocol between eye banks providing the corneal grafts or be due to differences in the postoperative detection of corneal guttae. Use of only specular microscopy for the detection of postoperative guttae formation may on the one hand result in an overestimation of observed cases because not all 'dark spots' are corneal guttae[19] but may on the other hand also result in falsely labelling dark spots on the specular microscopy images as 'nonguttae' as previously done with case #2 (Fig. 1) in a previous study of our group.[19] Confocal microscopy is a more reliable tool for identifying corneal guttae in eyes that show 'dark spots' on specular microscopy images, but there might still be a possibility to mistake pseudoguttae for corneal guttae as both show similar appearances on confocal microscopy images.[20] The presence of pseudoguttae, however, can be ruled out if the guttae are observed at consecutive follow-up visits because pseudoguttae usually do not persist for a prolonged period.[20]

The observed location and density of the corneal guttae on the DMEK grafts showed a lot of variability within this case series. As corneal guttae usually manifest in the corneal center,[21] in all cases guttae occurred in various extents in the center of the DMEK graft, but corneal guttae were also observed in the paracentral regions. Interestingly, in 1 DMEK graft, a higher density of corneal guttae could be observed paracentrally than centrally (Fig. 4). Although this could potentially be caused by an eccentric graft preparation, it seems more likely in this case that the paracentral guttae location is related to the graft characteristics itself because a 9.5-mm DMEK graft diameter was used, and no decentered graft trephination was reported by the eye bank during the graft preparation.

The progression of the observed guttae also varied among patients. Half of the eyes showed an increase in the number of guttae over time and progression occurred centrally and paracentrally. However, not all paracentral regions were equally affected by guttae progression, and although in the same areas almost confluent guttae were observed, other areas showed only isolated, small guttae (Fig. 2). What causes some grafts to show a progression in guttae density over time while others do not, is not yet known. It might be speculated that some donor grafts may have a genetic predisposition, but it might also be related to patient factors such as the aqueous humor composition or other stress factors or a combination of all factors.

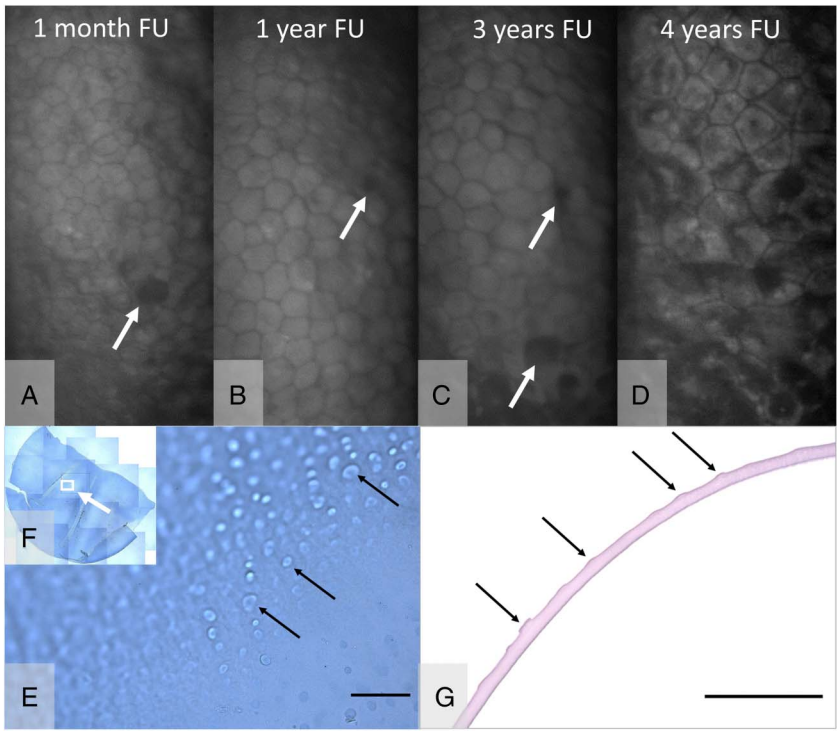

FIGURE 5. Specular microscopy images of case #7 and light microscopy and histology images of the removed DMEK graft. A–C, Postoperative central specular microscopy images of case #7 show only small isolated corneal guttae (white arrows) until the 3-year follow-up. D, At the 4-year follow-up, the DMEK graft had started to fail, and the endothelial cells were enlarged and polymorphic with activated nuclei. At 56 months postoperatively, the patient underwent repeat DMEK for secondary graft failure and the removed primary DMEK graft was analyzed by (E) light microscopy and (G) histology. In the inset (F), the white rectangle (white arrow) indicates the area on the graft that is shown in (E). Black arrows in (E) and (G) point to corneal guttae. Scale bars correspond to 100 μm.

The effect of the corneal guttae on clinical outcome and graft survival also remains a matter of speculation. Borderie et al reported that PK grafts with grouped guttae had lower graft survival probabilities,[6] whereas Nahum et al and Schönit et al did not find an effect of postoperative guttae on PK graft survival.[10,15] For DMEK, also no effect of guttae on graft survival was reported.[14] In our case series, 2 of 13 grafts (15%) failed, but because this is a small case series, this might not be representative for the actual graft survival probability in the presence of guttae, which might be comparable to the graft survival probability observed in a large DMEK cohort (90% at the 5-year follow-up and 85% at the 10-year follow-up).[22]

Corneal guttae are known to affect endothelial cells,[3] but the effect of the observed corneal guttae on postoperative ECD is difficult to quantify because endothelial cell counts on specular microscopy images in the presence of corneal guttae do not tend to be reliable due to a high degree of variability in cell density.[23,24] For best-corrected visual acuity, 10 of 11 eyes without graft failure had a best-corrected visual acuity of 0.9 (decimal) or better at the last available follow-up which is comparable to DMEK outcomes reported earlier.[22,25,26]

In conclusion, corneal guttae can occur after DMEK including in eyes operated for indications other than FECD. The postoperative occurrence of guttae is most likely due to guttae on the donor graft that were not detectable by routine slit-lamp and light microscopy evaluation in the eye bank. Postoperative guttae density varies among patients and guttae progression. The overall incidence of guttae occurrence seems to be low and especially small isolated guttae do not seem to affect clinical outcomes.

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