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Anterior chamber fibrin reaction during Descemet membrane endothelial keratoplasty

Liem Trinh [a,*], Nacim Bouheraoua [a,b], Marc Muraine [c], Christophe Baudouin [a,b,d]

[a] CHNO des Quinze-Vingts, IHU Foresight, INSERM-DGOS CIC 1423, 28 Rue de Charenton, F, 75012, Paris, France
[b] Sorbonne Université, INSERM, CNRS, Institut de La Vision, 17 Rue Moreau, F, 75012, Paris, France
[c] Department of Ophtalmology, Hospital Charles Nicolle, Rouen, France
[d] Department of Ophthalmology, Ambroise Paré Hospital, AP-HP, University of Versailles Saint-Quentin-en-Yvelines, Boulogne-Billancourt, France

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ABSTRACT

Purpose: To report a series of five cases of intraoperative spontaneous anterior chamber fibrin reaction during Descemet Membrane Endothelial Keratoplasty (DMEK).

Methods: We retrospectively collected demographic data and data for ocular disease history for each patient. Donor age, preoperative graft endothelial density, surgical complications on surgery and intraoperative OCT videos, intraoperative management and outcome were assessed. The same standardized DMEK technique was used for all patients.

Results: We report intraoperative fibrin formation in five eyes subjected to DMEK. Three pseudophakic eyes underwent single DMEK, and the other two underwent combined DMEK and cataract surgery. In one case, a fibrin filament was observed before graft insertion, with multiplication during surgery, whereas, in the other four cases, strands of fibrin from the iris appeared after graft insertion. This complication resulted in graft failure in four cases (80%). No recipient- or donor-related risk factor was identified.

Conclusions and importance: The anterior chamber fibrin reaction is a very uncommon complication of DMEK. The underlying pathophysiological mechanisms remain unknown, but analyses of surgical videos and intraoperative OCT suggest iris involvement. This phenomenon may be induced by chronic subclinical anterior chamber inflammation, due to a blood-aqueous barrier breakdown associated with acute iris trauma during surgery. Thus, intraoperative microtraumatism of the iris should be avoided.

1. Introduction

Descemet membrane endothelial keratoplasty (DMEK) has become the benchmark treatment for endothelial diseases, such as Fuchs' endothelial corneal dystrophy (FECD), thanks to excellent visual outcomes, speed of recovery and low rates of graft rejection.[1–3] The surgical procedure is now well standardized, and various intraoperative and postoperative complications, such as graft detachment, difficulty in graft unfolding/positioning, anterior chamber hemorrhage, increased intraocular pressure, immunologic graft rejection and iatrogenic primary graft failure due to placement of an upside-down graft, have been described in detail.[4] One of the most challenging steps in this procedure is the unfolding of the Descemet membrane graft in the recipient eye. Any difficulty unrolling the donor graft (tight roll, deep or shallow anterior chamber, anterior synechia) can lead to the failure of keratoplasty. Spontaneous anterior chamber fibrin formation during DMEK has been summarily mentioned in the past only twice in publications but little is known about its actual frequency and mechanisms.[5,6] More recently, Benage and coworkers reported specifically a first series of cases of intraoperative fibrin formation during DMEK, making surgery longer and more difficult.[7] The authors suggested that bleeding in the anterior chamber was induced by iridectomy or intraoperative hypotony, but the mechanisms remain unknown. We report a series of cases of intraoperative fibrin reaction, describe surgical issues and discuss pathophysiological hypotheses based on surgery videos and intraoperative OCT scans with surgery video capture, with a view to identifying risk factors for preventing this rare complication.

* Corresponding author. Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, 28 rue de Charenton, Paris, 75012, France.
E-mail address: trinhdinhliem@gmail.com (L. Trinh).

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2. Methods

We performed a retrospective study of data collected during consecutive DMEK procedures performed by one surgeon (L.T.) in which the intervention was complicated by intraoperative spontaneous anterior chamber fibrin reaction. We recorded demographic data for the patients, together with information about prior cataract surgery, concomitant treatments, including anticoagulant use, corneal endothelial disease, and the nature of the surgery (single DMEK or combined DMEK-cataract surgery). Donor age, preoperative graft endothelial density, time on the corneal graft waiting list before surgery, the description of the surgical complication with fibrin formation on the surgery video, intraoperative management, outcome and final visual acuity were assessed. This study was performed in accordance with the Declaration of Helsinki, and patients gave informed consent for the collection and analysis of their data.

2.1. Surgical technique

The cornea was excised from the donor, and the graft was then stored initially in organ culture medium CorneaPrep (Eurobio, Courtaboeuf, France) and then in CorneaMax (Eurobio) at 31 °C, before the assessment of endothelial cell morphology and viability. It was finally stored in CorneaJET (Eurobio) for deturgescence, for three days, immediately before surgery.

The donor Descemet membrane graft was prepared as previously described.[3] The donor graft was stained with trypan blue (Visionblue, D. O.R.C International, Zuidland, the Netherlands) in balanced salt solution (BSS) after donor preparation.

The same standardized DMEK technique was performed on all patients, by the same surgeon. Surgery was performed on all eyes under local sub-Tenon anesthesia (1 mL of 2% xylocaine).

The recipient endothelium was stained with trypan blue and descemetorhexis was performed with a reverse Sinskey hook over a diameter of 8.0 mm, under cohesive viscoelastic (ProVisc, Alcon Laboratories, Inc., Fort Worth, Texas, USA), through a 2.4 mm corneal incision. The viscoelastic was completely removed with the irrigation/aspiration cannula of a phacoemulsification device (Centurion, Alcon Laboratories). The rolled donor Descemet membrane was aspirated into a specific glass injector (Geuder AG, Heidelberg, Germany), for insertion into the recipient anterior chamber, the depth of which was maintained by BSS injection through a secondary incision, to prevent intraoperative hypotony. Graft orientation was assessed by intraoperative optical coherence tomography (OCT) (Rescan®700, Carl Zeiss Meditec, Iena, Germany). Peripheral iridectomy was performed only at the end of surgery, after the graft had been completely unfolded in the right orientation, and an air bubble was injected. For combined DMEK-cataract surgery, phacoemulsification was performed first, and descemetorhexis was performed just after intraocular lens (IOL) implantation, while viscoelastic was still present. A miotic agent, acetylcholine (Miochol, Laboratoire Chauvin, Montpellier, France), was injected into the anterior chamber when the surgeon considered it useful, before donor graft insertion, to induce miosis, in two eyes of the five described cases. The rest of the procedure was as for single DMEK surgery.

2.2. Surgery videos

Complete surgery videos, with intraoperative OCT videos, were recorded with an OPMI Lumera® 700 microscope with OCT Rescan® 700 (Carl Zeiss Meditec, Iena, Germany) for four patients. These videos were analyzed retrospectively, to elucidate the mechanisms of fibrin formation. Screen captures including intraoperative OCT scans were performed to show sequences of surgery, the appearance of the fibrin strands and the timing of their appearance.

2.3. Statistical analysis

Results are presented as the mean for continuous variables and as proportions (%) for categorical variables. Statistical analyses were performed with Excel 2011 software (Microsoft Corp).

3. Results

We identified five eyes (from five patients) from a total of 133 eyes (from 106 patients) treated with the same standardized DMEK technique since 2016, for which intraoperative spontaneous anterior chamber fibrin reaction (3.7%) was observed. DMEK had previously been successfully performed on the contralateral eye in one of these five patients. The characteristics of these patients and of the surgery performed are summarized in Table 1. The median age of the patients was 63 years (range: 54–77 years), and there were four women and one man. Four patients underwent DMEK for FECD, and one underwent surgery for endothelial decompensation on posterior polymorphous corneal dystrophy (PPMD) after cataract surgery. None of the patients had preoperative iris damage. None of the five patients had previous comorbidities which could favor anterior chamber inflammation such as glaucoma, neovascularization or pseudoexfoliation syndrome. None of the five patients take associated drugs like tamsulosin or eye drops and especially no eye drops based on prostanglandins before the surgery but one patient was on anticoagulant (rivaroxaban, discontinued 3 days before surgery). Three of the five eyes were pseudophakic and underwent single-procedure DMEK. The remaining two eyes were phakic and underwent combined DMEK and cataract surgery. On the 133 eyes subjected to DMEK, 27 had combined surgeries (20,3% of combined surgeries on all DMEK in our series) while in our five DMEK surgeries complicated of fibrin reaction, 2 were combined surgeries (40% of DMEK with fibrin). Spontaneous fibrin formation occurred in 3 of 106 single DMEK (2,8% of all single DMEK), and in 2 of 27 combined DMEK (7,4% of all combined DMEK).Trypan blue was injected into the anterior chamber in all patients, together with viscoelastic for descemetorhexis. Only two of the patients received miochol injections. The median age of the donors was 77 years (range: 58–81 years), and the median preoperative endothelial cellular density (ECD) of the graft was 2446 cells/mm^2 (range: 2289–3533 cells/mm^2). None of the patients had any surgical complications of cataract surgery, such as capsular rupture, vitreous prolapse or zonular disinsertion, but one patient who underwent combined DMEK-cataract surgery suffered from iris prolapse during cataract surgery, leading to iris atrophy in front of the primary incision. Median time on the corneal graft waiting list before surgery was 9 months (range: 5–22 months).

In all five eyes, following the insertion of the donor graft into the anterior chamber, mobilization and unfolding were very difficult. In each of these eyes, we observed strands of fibrin from the iris and unfolding donor graft, in the form of a filamentous gel (Fig. 1–3), preventing intracameral movement. In four cases, this phenomenon appeared after graft injection, when the surgeon tapped on the cornea to unfold the rolls. However, in the remaining eye, a filament of fibrin from the iris was already visible during removal of the viscoelastic before graft insertion (Fig. 1D), with amplification of this phenomenon after pressure was placed on the cornea during unrolling (Fig. 1H and I). Unscrolling time was not measured in our study, but fibrin formation occurred more frequently after long repeated tapping movements and long unscrolling time. Fibrin was not always initially visible, but its presence was demonstrated by a lack of mobilization of the graft, which seemed to be stuck to the iris. We were able to increase filament visibility, by injecting trypan blue to stain the filaments (Fig. 2A). The strands of fibrin came from the iris, as observed on the intraoperative OCT (Fig. 2C). For patient 3, Fig. 3 showed pigmented network of filaments of fibrin clearly native from the entire surface of the iris. Stretching of these strands with the cannula completely mobilized the iris, so there were no doubt about fibrin strand emerged from the iris.

Table 1
Patients, surgical and donor graft characteristics.

Patient	Age (years)	Anticoagulant	Endothelial disease	Preoperative BCVA	Combined or single DMEK	Miochol injection	Graft failure	Final BCVA	Donor graft age (years)	Time on corneal graft waiting list (months)
1	68	N	PPMD	20/63	S	Y	Y	HM	81	5
2	54	N	FECD	20/32	C	N	N	20/25	58	20
3	63	N	FECD	20/200	C	N	Y	20/200	59	8
4	62	N	FECD	20/32	S	Y	Y	CF	77	22
5	77	Y	FECD	20/63	S	N	Y	20/32	79	9
Median	63								77	9

BCVA: Best corrected visual acuity; **ECD:** Endothelial cellular density; **N:** No; **PPMD:** Posterior polymorphous corneal dystrophy; **S:** single DMEK surgery; **Y:** Yes; **HM:** Hand motion; **FECD:** Fuchs' endothelial corneal dystrophy; **C:** combined DMEK and cataract surgery; **CF:** Count fingers.

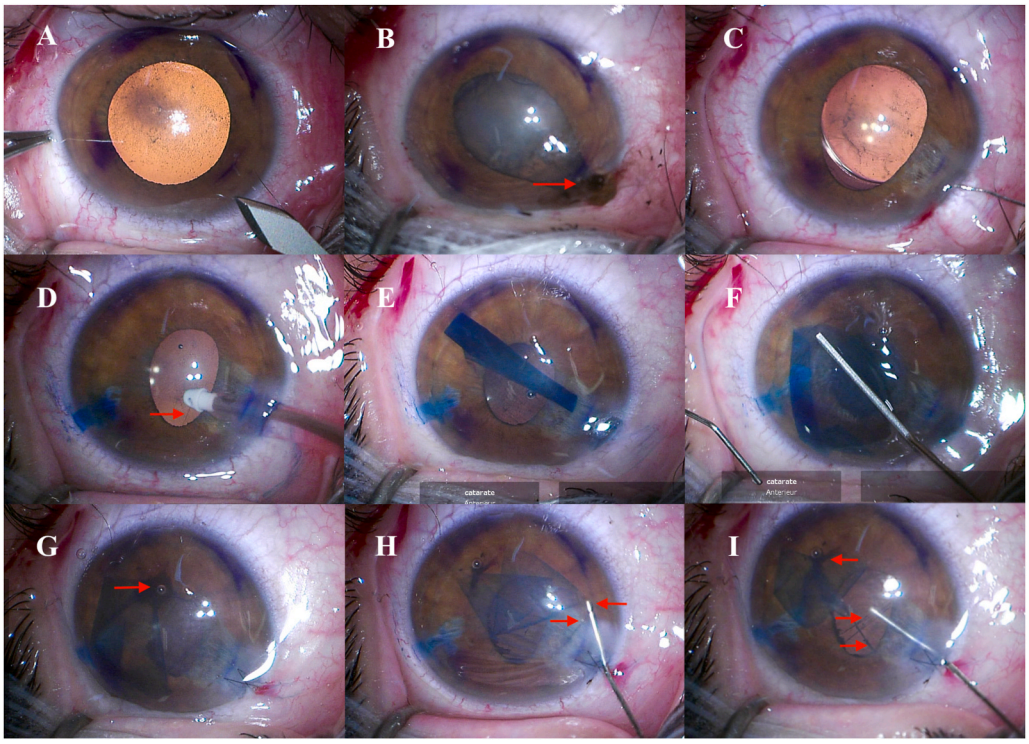

Fig. 1. Description of fibrin formation during combined DMEK-cataract surgery for patient 2. A. At the beginning of surgery, no fibrin or pre-existing iris damage was observed. **B.** After hydrodissection during cataract surgery, iris prolapse occurred in the main incision (red arrow), provoking iris atrophy. **C.** Cataract surgery was performed without incident, and IOL was injected in the capsular bag. There was no capsular rupture, vitreous prolapse or zonular disinsertion. **D.** During removal of the viscoelastic with an irrigation/aspiration cannula and before graft insertion, we aspirated a filament of fibrin coming from the iris (red arrow). **E.** The Descemet's membrane roll was inserted in the anterior chamber. **F.** Tapping movements on the cornea to unfold the Descemet's membrane graft. **G.** Clod of pigmented fibrin from the iris (red arrow), glued to the graft. **H.** Strands of fibrin (red arrows) from the atrophic part of the iris, with an elastic consistency, adhered to the endothelial graft. **I.** Descemet's membrane graft trapped in the pigmented clod and filaments of iris fibrin (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

During the surgery irrigation and aspiration were tried and the strand appeared to be tethered to the iris. We were unable to remove these networks of fibrin, due to their elastic consistency (Fig. 1H, 2B and 3B), and for fear of damaging the graft. It was not possible to unfold the graft completely in any of these cases. After a number of attempts, an air bubble was injected under the partially unfolded graft. Only one of the five patients displayed a full recovery of corneal transparency, despite the graft being folded over on itself, with a final visual acuity of 20/25. The other four eyes (80% of this series) displayed an increase in corneal edema and were subjected to a second keratoplasty: DMEK in two cases, and penetrating keratoplasty (PK) in the other two. Fibrin formation also occurred during the second DMEK intervention, but to a lesser extent, and it was possible to unfold the graft. Peripheral iridectomy was performed only at the end of surgery, with fibrin formation occurring before iridectomy in each case. No intraoperative intraocular hemorrhage was observed.

4. Discussion

We describe here five cases of spontaneous intraoperative fibrin reaction during DMEK, for which we investigated the underlying mechanisms of formation by analyzing videos of the surgical procedures. A long duration of subchronic intracameral inflammation in FECD associated with iris traumatism appeared to favor intraoperative fibrin formation from iris tissue.

This complication has been briefly reported only twice in the past,[5,6] and seems to complicate intraocular manipulation of the graft. More recently, Benage and coworkers reported specifically the first case series of 32 eyes presenting fibrin reaction.[7] The underlying pathophysiological mechanisms remain unknown, but this uncommon intraoperative complication makes it more difficult to unfold the graft and can lead to graft failure. The difference with this previous article is the addition of the first descriptive photos and OCT images of this complication. The incidence of this complication in our patients (3.7% of patients undergoing DMEK) was similar to that reported by Benage and coworkers. This is a higher frequency than might have been expected given the lack of description of this complication in previous studies. However, this complication may have a severe impact, leading to 80% graft failure in our series. Once the strands of fibrin appeared, it became impossible to mobilize and unfold the rolls. Benage and coworkers put forward several

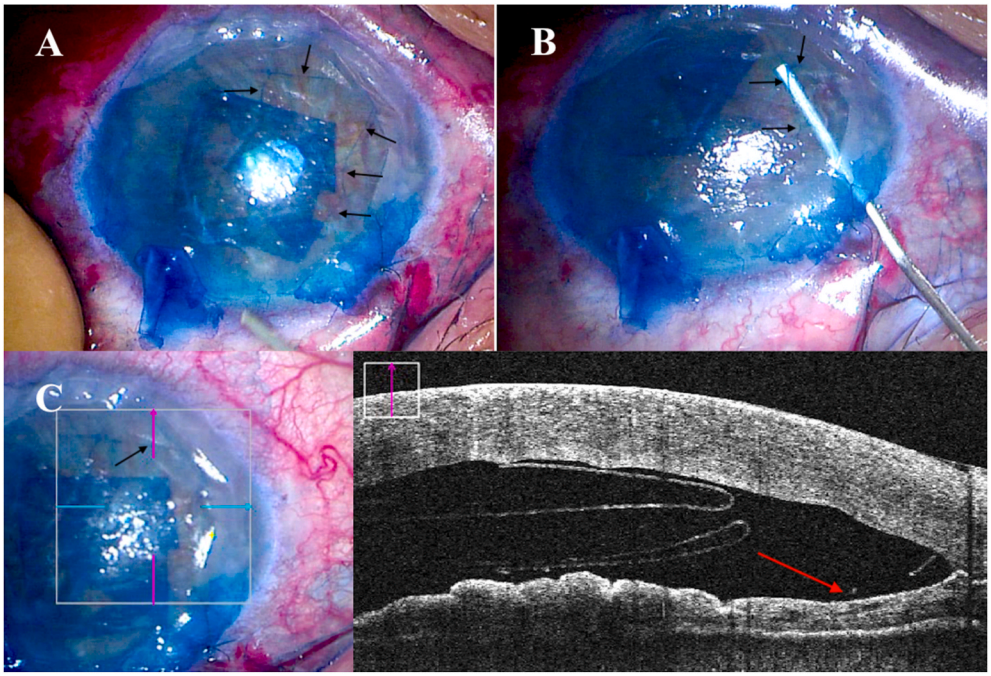

Fig. 2. Description and localization of fibrin filaments in patient 1.
A. Network of filaments of fibrin (black arrows) on the iris, stained with trypan blue, enveloping the Descemet's membrane graft. **B.** Strands of fibrin at the end of the cannula (black arrows) with an elastic consistency. **C.** Intraoperative OCT image showing the localization of fibrin filaments (black arrow on the micrograph) on the surface of the iris (red arrow in the corresponding OCT scan from Rescan®700, Carl Zeiss Meditec, Iena, Germany). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

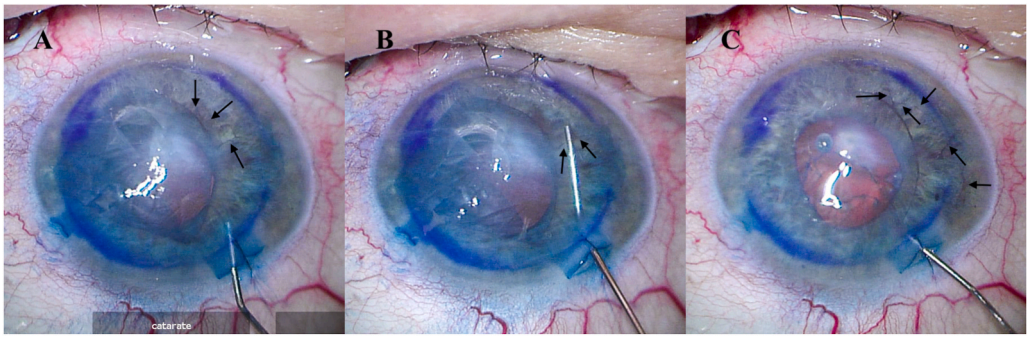

Fig. 3. Description of strands of fibrin in patient 3.
A. Pigmented network of filaments of fibrin (black arrows) surrounding the endothelial graft and preventing mobilization. **B.** The cannula could not section any of these strands (black arrows), due to their elasticity. **C.** These filaments could be seen over the entire surface of the iris (black arrows).

possible explanations for this phenomenon: anticoagulation therapy before surgery, hemorrhaging during iridectomy and a reflux of serum through the trabeculum due to intraoperative hypotony. We did not confirm these hypotheses. In our series, only one of the five patients (20%) was on anticoagulant therapy. Moreover, none of the patients had bleeding or iridectomy before fibrin formation, and we systematically tried to minimize hypotony by maintaining anterior chamber volume during injection of the donor graft. We were unable to identify any risk factors from the patients' history, characteristics, known medical conditions, current treatment or related to the donor graft. We cannot impute the origin of fibrin formation to the donor graft either, as fibrin filaments were visible before graft insertion in one case (Fig. 1D). These filaments cannot be attributed to the vitreous either, as there were no complications of cataract surgery.

The fibrin seemed to originate from the iris on intraoperative OCT, and appeared to have been induced by microtraumatisms of the iris, due to tapping movements or intraoperative iris prolapse, as the iris enveloped and adhered to the rolled donor membrane with filaments. Progressive late decompensated FECD may generate chronic anterior chamber subinflammation, as some studies have reported high levels of cytokines in the aqueous humor in patients undergoing bullous keratopathy (BK) and FECD.[8–11] A chronic inflammatory environment may promote fibrin formation via blood aqueous barrier (BAB) breakdown in the iris capillary endothelium. It is also known that pre-existing iris damage is associated with the failure of Descemet's stripping automated endothelial keratoplasty (DSAEK), with lower levels of ECD, probably due to disruption of blood-aqueous barrier (BAB) in the iris, leading to postoperative intraocular inflammation,[12] and associated with high levels of cytokines in the aqueous humor.[13]

Patients with anterior uveitis are known to have lower levels of ECD.[14] Alfawaz et al. described a correlation between ECD and the duration of active inflammation, which also seemed to alter endothelial function. Maximum flare was associated with lower levels of ECD, so inflammatory mediators, such as cytokines, may injure endothelial cells.[14] This suggests that BK may have an inflammatory component that also contributes to the degradation of ECD. In normal conditions, the anterior chamber is an immunosuppressive environment, but, in BK, a dysfunction of endothelial immunomodulation may cause a breakdown of the BAB and chronic subinflammation.[8] This disruption of the BAB would favor the fibrin reaction during DMEK surgery, potentially triggered by acute iris trauma.

Fibrinogen is a soluble fibrous protein normally present in human blood plasma, which is converted to fibrin by thrombin, after activation by vessel wall damage or activated blood cells.[15] Fibrin is an insoluble

filamentous protein, that forms blood clots so as to prevent blood loss and promote wound healing.[15] The fibrin found in the anterior chamber in our cases may come from fibrinogen in iris vessels, and its formation may be explained by disruption of the BAB and acute vessel wall injury in the iris capillary endothelium. Intraoperative microtraumatisms of the iris, during the tapping of the recipient corneal surface during DMEK, for example, may aggravate this phenomenon, so we recommend to shorten unscrolling time as much as possible to decrease intraoperative iris microtraumatisms. We were unable to identify any risk factors for fibrin formation, but the duration of active inflammation and the severity of FECD may have an effect. The number of cytokines for which levels were high was greater in cases of BK than in undecompensated FECD.[8] BK is probably associated with chronic long-term anterior chamber inflammation, and a long waiting time until DMEK may increase the risk of intraoperative fibrin reaction. The combination of cataract surgery with DMEK may also be a risk factor, as such interventions may induce a higher level of inflammation and more iris trauma than single-procedure DMEK. However, we were unable to confirm this hypothesis in our patients, as fibrin formation occurred in three patients undergoing single-procedure DMEK and to undergoing combined surgery. We initially thought that miochol might be involved, as a miosis-induced extrusion of soluble protein from the iris stroma has been reported.[16] However, the fibrin reaction occurred in the absence of miochol injection (in 3 eyes on 5). Finally, we recommend that surgeons should take precautions to preserve iris integrity during surgery, as any iris damage, including iris prolapse, can increase the likelihood of BAB breakdown and increase intraoperative inflammation. To prevent this inflammatory reaction in anterior chamber, a preoperative treatment of non-steroidal anti-inflammatory eyedrops such as nepafenac or even corticosteroid eyedrops could be initiated especially in patients with late decompensated inflammatory FECD.

Postoperative fibrin formation has frequently been described after cataract and glaucoma surgery,[17–22] but intraoperative fibrin formation has only very rarely been reported. Intracameral recombinant tissue plasminogen activator (r-TPA) is used as a preventive and curative treatment for postoperative fibrin formation.[18–20,23,24] The intracameral injection of 25 μg r-TPA seems to be safe and effective for the treatment of postoperative anterior chamber fibrin formation.[20,23] The time required for complete fibrin dissolution ranges from 1 h to one day.[20] Thus, r-TPA injection may be beneficial as an intraoperative treatment to induce fibrinolysis.

Intraoperative fibrin filaments can be visualized with trypan blue, as described here, or with intracameral triamcinolone acetonide staining, as in complicated cataract surgery, to increase the visibility of vitreous prolapse. Moreover, triamcinolone acetonide has anti-inflammatory properties of potential value in this inflammatory environment. Anterior vitrectomy could also be an interesting option to remove the strands of fibrin in the case they appear before graft injection.

The mechanisms underlying the intraoperative fibrin reaction remain unknown, but we can, nevertheless, make a number of recommendations for management strategies. As BK was probably associated with chronic long-term anterior chamber inflammation, late decompensated FECD may be a risk factor for fibrin reaction. A preventive preoperative non-steroidal anti-inflammatory eyedrops treatment could be initiated some weeks before DMEK, especially in patients with late decompensated inflammatory FECD. Then, intraoperative use of intracameral triamcinolone acetonide could help to visualize fibrin formation just before graft insertion and remove them with anterior vitrectomy. Iris trauma during surgery should be minimized, to prevent bleeding of the iris. If performed, peripheral iridectomy should take place just before air injection, and the graft should be unfolded with only a very small number of soft tapping movements on the cornea and short unscrolling time. Finally, if strands of fibrin appear despite these precautions, the intracameral injection of r-TPA could be tested.

5. Conclusions

In conclusion, we report here a series of five eyes displaying intraoperative fibrin formation during DMEK. We hypothesize a major role of iris involvement. Further reports of fibrin reaction during DMEK will be required to determine precisely the pathophysiological mechanisms underlying this uncommon complication. Injection of intracameral triamcinolone acetonide may detect precociously fibrin reaction, and avoiding trauma to the iris may help to prevent future cases of this complication.

Patient consent

The collect of data was performed with approval from our Institutional Review Board (IRB). Written consents to publish this case series were obtained. This case series does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

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