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ORIGINAL ARTICLE

Severe color change in corneal tattoos: Report of 3 cases

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Summary
Introduction. — Corneal tattooing is a noninvasive technique which appears relatively well-tolerated in the medium term. We report the cases of 3 patients with a significant change in the color of their tattoos performed over 5 years previously.
Patients and methods. — Three patients with a history of intracorneal tattooing several years previously were studied because of a significant change from their initial color. Each patient's file was reviewed with analysis of slit lamp photographs, OCT and specular microscopy.
Results. — All three patients experienced a significant color change in their tattoos between 5 and 6 years after surgery. The color had changed to golden-brown.
Discussion. — Retrospective analysis of the components of the tattoo ink found the presence of iron in the black pigment. We believe that pigments composed of iron oxide are transformed into golden-brown ferric iron oxide in the presence of oxygen in the aqueous environment. The presence of moderate corneal edema in these three cases of multioperated patients could explain, in these specific cases, the occurrence of oxidation typically not described.
Conclusion. — Corneal tattooing remains a simple and very interesting technique when partial or total absence of iris causes significant photophobia. However, the significant changes in color that we report more than 5 years later suggest removing iron from the dyes used for the cornea and limiting its use in cases of limited endothelial prognosis. A long-term evaluation of corneal tattoos appears necessary.

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Introduction

Corneal tattooing is a little-known but very useful technique in a large number of clinical situations [1—14]. It was initially proposed for aesthetic purposes to camouflage white corneal scars in eyes with no visual potential. The indications then expanded to include treatment of iris abnormalities (post-traumatic or post-surgical partial or total aniridia) [15—26] or more rarely limbal dermoids [27—30] or even leukocoria in blind eyes [31]. The literature included even more rare indications such as masking of the visual axis of one eye in certain cases of monocular or binocular diplopia refractory to all other treatment [32,33], or for reduction of pain and photophobia in bullous keratopathy [34—36] not amenable to corneal transplantation. More recently, corneal tattooing has even been proposed for aesthetic reasons to change eye color [37] and for refractive reasons in prebyopia [38]. Initial tolerability and biocompatibility have been reported to be satisfactory in the majority of cases at short and medium term, but long-term data are rare, since only one very recent study reports clinical results several years after performance of a tattoo [39]. The purpose of our study is to report and discuss the cases of three patients who received corneal tattoos and were seen several years later for recent significant color change.

Materials and methods

We report the cases of 3 patients (Table 1) who underwent intrastromal corneal tattooing several years previously to mask large post-traumatic or post-surgical iris defects and who presented several years later for a significant color change in their tattoos, which had turned golden-brown. Each patient had been tattooed by the same surgeon in the Rouen university medical center, using the same surgical technique and the same tattoo inks. Each patient underwent slit lamp photography preoperatively, immediately postoperatively and in the late postoperative period. On the last examination, we also performed for each patient: corneal pachymetry (Tomey, Nuremberg, Germany), specular microscopy (Nidek, France) and high-definition corneal OCT (Zeiss, Oberkochen, Germany).

Surgical technique

The technique has been previously described [23]. After marking the central six millimeter zone of the cornea for placement of the new pupil, an intrastromal lamellar dissection is performed anterior to the iris defect with a crescent blade, then a lamellar dissection spatula. The surgeon takes care during this dissection to not enter into the central 6 mm zone. This intracorneal delamination creates a stromal pocket into which the ink is deposited so as to tattoo the corneal. The dye is in the form of a paste; it is slipped into the stromal pocket with a micro-manipulator.

The dyes used were cosmetic cream pigments from the Biochromaderm® line of Biotic Phocea laboratory, France, and are available in 2 ml jars. They have been C.E. marked for medical use. Numerous colors are available, which can be mixed, even within the stroma, so as to obtain the desired tint. In our study, we used only Charcoal®, Brown® and White®. We systematically used the black pigment for its better masking effect than the other pigments, thus improving the disabling photophobia for the patients. We then added the two other pigments to achieve a satisfactory aesthetic result.

Results

Patient 1

We report the case of a 67-year-old woman who had undergone corneal tattooing for post-traumatic total aniridia of her left eye 6 years previously. She presented for a gritty sensation in the left eye along with decreased visual acuity for several weeks. This patient had been on topical two-drop therapy for post-traumatic ocular hypertension for several years (beta-blocker and prostaglandin).

Examination of the left eye revealed corrected visual acuity of 1/20 and intraocular pressure of 16 mmHg. Slit lamp examination showed mildly inflamed conjunctiva, a brown to golden 360° corneal tattoo and moderate diffuse corneal edema. The epithelium was irregular, but fluorescein staining was negative. Comparing our examination to the immediate postoperative slit lamp photo, we noted a clear color change in the tattoo, which had initially been blue due to the mixture of black and white pigments, as well as migration of pigment into the pupillary zone.

Central corneal pachymetry was 600 μm, and central specular microscopy was impossible due to the moderate corneal edema.

The high-definition corneal OCT image indicated that the stromal tunnel where the pigment had been inserted was 190 μm from the corneal surface. Also noted in certain locations in the cornea was pigment which had migrated sub-epithelially to less than 50 μm from the surface. The

Table 1 Description of the 3 patients who had undergone corneal tattooing and developed a significant color change over time.

Patient	Sex	Age(Years)	Eye	Indication	Year of tattooing	Pigment colors	Associated surgeries
1	F	67	Left	Post-traumatic iris defect	2011	Black White	None
2	M	44	Left	Post-surgical iris defect	2012	Black White	None
3	F	50	Right	Post-traumatic iris defect	2012	Black Brown	Iridoplasty

preoperative photos also show a suggestion of temporal corneal edema anterior to the old iris trauma, suggesting a fragile cornea at the time of tattooing. After short-term anti-inflammatory treatment, corrected visual acuity improved to 6/10 and has been stable for the subsequent 6 months (Figs. 1 and 2).

Patient 2

This is a 45-year-old man with a history of bilateral congenital cataract surgery in childhood, who was left aphakic. He had undergone corneal tattooing of his left eye in 2012 for extensive post-surgical aniridia resulting in disabling photophobia. Black and white pigments had been mixed to mimick a blue iris. The postoperative course was unremarkable. He saw us 5 years later for a burning discomfort in his left eye, recurrent photophobia and tearing for several months. His only treatment had been topical pressure-lowering drops in the left eye (beta-blocker).

Examination revealed visual acuity of hand motions in the left eye, which was actually stable for this profoundly amblyopic eye. Slit lamp examination showed an uninflamed conjunctiva; the initially blue corneal tattoo had turned brown, and the pigment had migrated into the pupillary zone. Moderate diffuse corneal edema was also visible and evidenced by central corneal pachymetry of 610 μm which was resulting in an irregular corneal surface. Endothelial cell density could not be evaluated due to this edema.

The high-definition corneal OCT image indicated that the stromal tunnel where the pigment had been inserted was 250 μm from the corneal surface, but nasally, a layer of pigment was present very superficially (Figs. 3 and 4).

Patient 3

This was a 50-year-old woman with a history of trauma to the right eye in childhood requiring cataract surgery at age 7 years and secondary IOL implantation in Germany at age 17 years. She had undergone corneal tattooing in the right eye on our service in 2012 for aesthetic and functional reasons so as to reduce her photophobia. Her tattoo had initially been dark brown, formed by a mixture of black and brown pigments.

We saw her again in 2017, thus 5 years after her tattooing surgery. Visual acuity was still 6/10, the same as after the tattoo. Slit lamp examination showed pigment diffusion from her tattoo into the pupillary zone as well as a color change, which had become more golden-brown in comparison with the immediate postoperative photographs. Central corneal pachymetry was 600 μm, and central specular microscopy reported a density of 1000 cells/mm^2.

The high-definition corneal OCT image indicated that the stromal tunnel where the pigment had been inserted was situated approximately 260 μm from the corneal surface. As in the preceding patients, the pigment had migrated subepithelially in certain spots (Figs. 5 and 6).

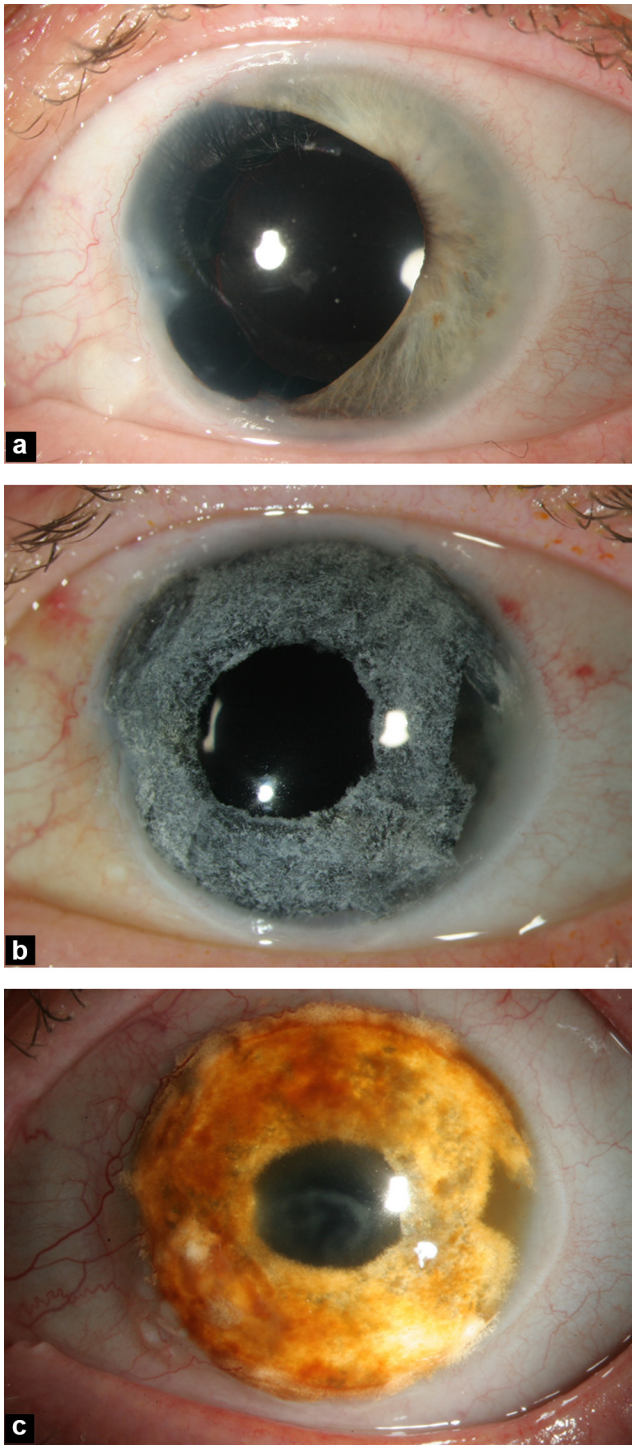

Figure 1. Change in clinical appearance of operated eye (patient No. 1): a: preoperative appearance; b: immediate postoperative appearance of corneal tattoo, mixing black and white pigments to mimick a blue iris; c: postoperative appearance 6 years after corneal tattoo, which has turned rusty brown.

Discussion

The efficacy of corneal tattooing is unequivocal for a certain number of ophthalmologic indications, while its tolerability remains in question. Thus, tattooing of the ocular surface after simple de-epithelialization is no longer performed, due to numerous reported cases of ocular irritation [40—42]. Since then, the tattoo ink has been deposited deeper in the corneal stroma, either by micropuncture techniques (needle or tattooing machine) [1,3,5,10,35,43], or into a

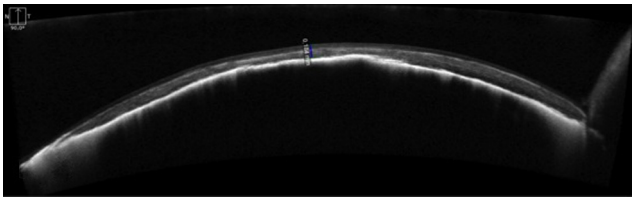

Figure 2. High-definition corneal OCT image with various measurements of corneal thickness (patient 1).

dissected intrastromal pocket performed with a spatula, as we typically do, or more rarely by femtosecond laser [4,15,16,18,19,31,37,44]. The deeper location of the dye allows for a less irritating tattoo which is more durable over time, and also allows for mixing of pigments.

The first dyes used in corneal tattooing included China ink [34], India ink [26,45], gold dust or other metallic powders, organic dyes, then later metal salts [10,40,46] such as gold chloride, silver nitrate and platinum chloride, which led to fewer inflammatory reactions. More recently, micronized mineral pigments have been developed in various colors such as carbon black, ferric hydroxide, iron oxide, ferric oxide, titanium dioxide, phthalocyanide, allowing intrastromal corneal tattoos to be performed in various colors [16,19,22,36,47,48]. The various pigments may be easily mixed so as to obtain a color as close as possible to that of the patient's iris.

Numerous studies report very satisfactory aesthetic results [2,3,5,7,16,18,19,22,32,37,44,48] as well as good functional results with clear improvement in photophobia [16,18—20,23]. In the majority of cases, there is no significant postoperative inflammation [8,32,47,48]. Tolerability and biocompatibility of the various pigments has also been more or less satisfactory to date [47—49].

However, despite good patient tolerability, a few cases of complications have been reported, such as cases of failure, with persistent aesthetic or functional problems, or postoperative recurrences [3,5,39], pigment attenuation [3,5,10,15,22,39,42], pigment migration into the pupillary zone [8,15], inflammation [48], infection, irritation [3,41], neovascularisation [39] or healing problems with delayed epithelial healing [35]. Also noted has been a suggestion of intolerance to the magnetic field of MRI in certain patients [39]. The majority of studies report short-term complications. Only one study to our knowledge has just recently described this notion of long-term color change [39]. This is a study by Alio et al. published in 2017, reporting a 19% incidence of color change in corneal tattoos at long-term. In their discussion, the authors suggest a mechanism of oxidation-reduction of iron-based pigments as the cause of this phenomenon.

In our three patients with a rust-brown color change, two had received a mixture of black and white pigments, and one woman a mixture of black and brown pigments. The etiologic mechanism of this color change is difficult to determine, since it is probably multifactorial and patient-dependent. However, in reviewing the composition of the various pigments, we could see that the black Charcoal® pigment and the Brown® pigment which we had used are both mineral pigments composed in part of black ferrous oxide C177499, which is none other than tri-iron tetraoxide, or Fe_3O_4.

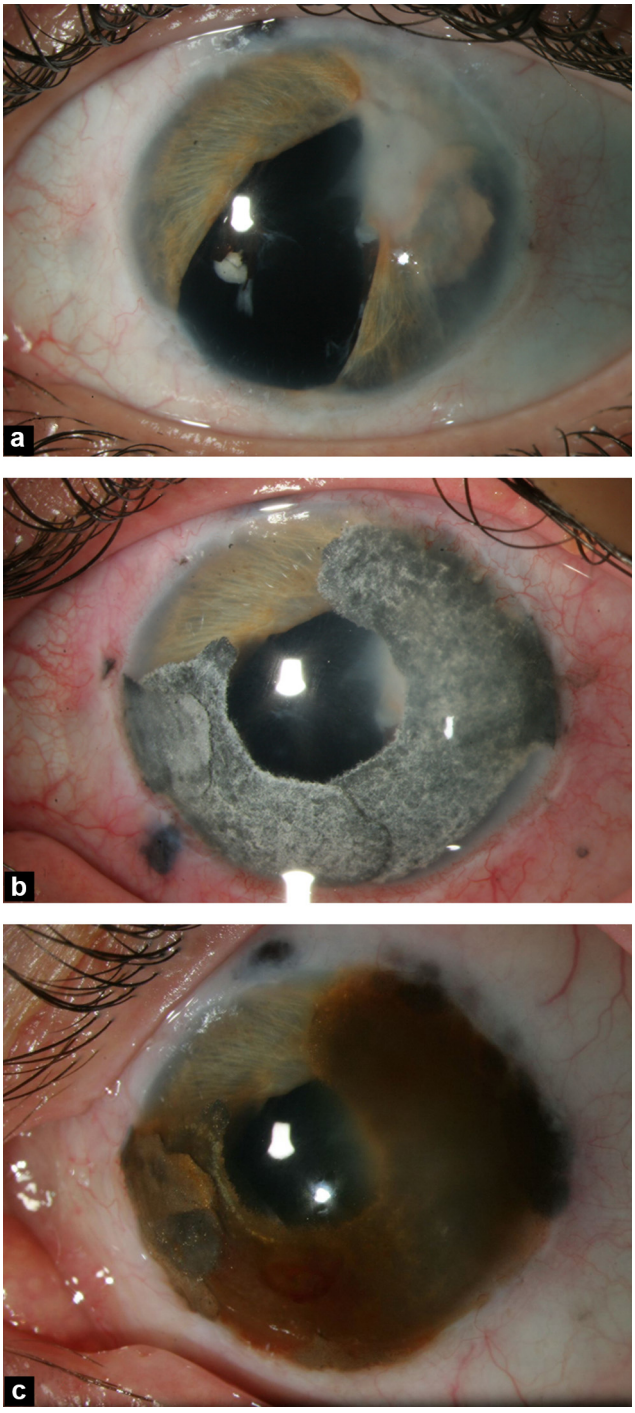

Figure 3. Change in clinical appearance of operated eye (patient No. 2): a: preoperative appearance; b: immediate postoperative appearance of corneal tattoo, mixing black and white pigments to mimick a blue iris; c: postoperative appearance 5 years after corneal tattoo, which has turned rusty brown.

According to chemical principles of iron oxidation-reduction, we found that tri-iron tetraxoxide, Fe_3O_4, in contact with oxygen, O_2, yields golden-brown ferric oxide, or Fe_2O_3. The reaction is as follows: $4\,Fe_3O_4 + O_2 = 6\gamma\,Fe_2O_3$. The cornea is an environment rich in oxygen, entering by direct contact with the air, by way of the tear film. In contrast, the skin is protected by the epidermis, which is

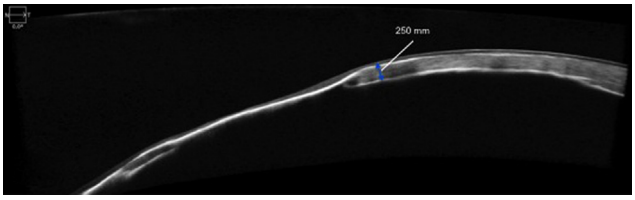

Figure 4. High-definition corneal OCT image with various measurements of corneal thickness (patient 2).

the most impermeable of all known biologic barriers, which explains why this phenomenon of pigment oxidation is not reported in the case of skin tattoos, and only their attenuation is reported. In addition, this reaction is favored by the humidity and acidity of the milieu and the presence of salt. Of course, in our three cases, the corneas were moderately edematous, around 600 microns, probably stemming from low endothelial cell density due to the initial trauma. It is quite logical that the increased hydration of the cornea in these cases might have favored diffusion of the ink as well as oxidation of the iron. In addition, the superficial location of the pigment in certain areas of the tattoo brings it closer to the oxygen in the tears. Thus, all the factors favoring oxidation were brought together in the corneal environment of these three patients, since the cornea is 80 to 90% water, has an acidic pH due to the action of carbonic anhydrase, and is rich in salt due to the mechanism of the Na-K ATPase pump.

Consequently, the black pigment turned progressively golden-brown and overshadowed the white pigment with which it had been mixed. When it had been mixed with brown, the aesthetic result was less noticeable.

The White® pigment is also a mineral pigment, but since it is composed of titanium oxide, no oxidation, and thus no color change, can occur if it is placed alone in the stroma.

It is interesting to note that the cases of color change are accompanied by pigment migration toward the center, which may result in a risk of secondary decreased visual acuity. By chance, in the technique which we describe, we always leave a central 6 mm corneal zone untattooed, which allows pigment migration over 1 to 2 mm with no visual effects. In addition, the visual acuity improved to 6/10 after the edema resolved in our case No. 1 and remained stable at 6/10 in case No. 3 despite the persistence of this central pigment migration. Case No. 2 was profoundly amblyopic and had never seen better than hand motions. We do not see central pigment migration in the absence of color change, and since we believe that it is corneal edema which favors pigment oxidation and migration, it is unlikely that the depth of pigment implantation plays a significant role. Certainly, deeper implantation would distance the pigment from the tear film, but we still prefer that the pigment be implanted at the junction of the anterior and middle thirds of the cornea so as to mask the posterior cornea, which is sometimes aesthetically disfigured, and also to avoid zones where the spaces between the collagen lamellae are looser. However, the risk of more superficial implantation than planned, resulting from manual dissection, is why some have proposed performing the dissection with a femtosecond laser. The advantage of this technique is to be able choose very precisely the depth of the cut and thus the zone of pigment deposition. The downside is that it is difficult to dissect a pocket in the far corneal periphery up to the limbus or when there are corneal scars.

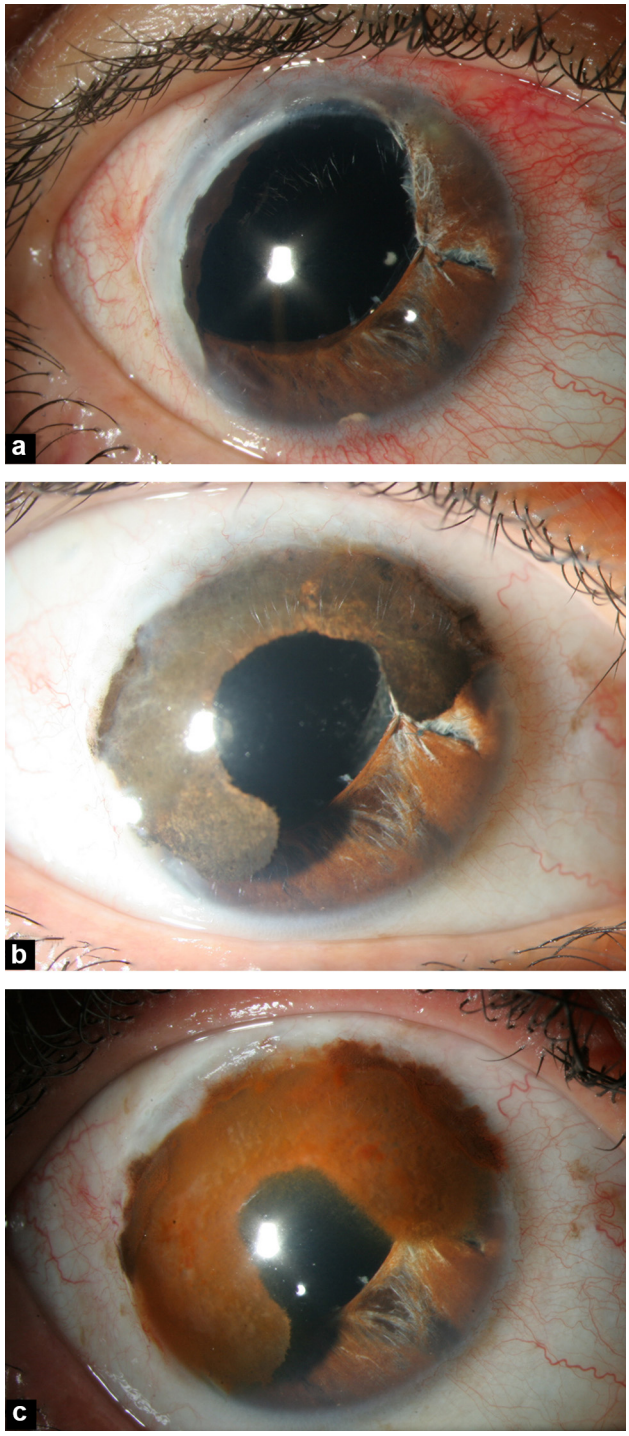

Figure 5. Change in clinical appearance of operated eye (patient No. 3): a: preoperative appearance; b: immediate postoperative appearance of corneal tattoo, mixing black and brown pigments to mimick a brown iris; c: postoperative appearance 5 years after corneal tattoo, which has turned rusty brown.

One might also consider using an ink with a less acidic pH so as to limit the oxidation phenomenon. Biotic Phocea laboratory (France) has actually introduced a new line of

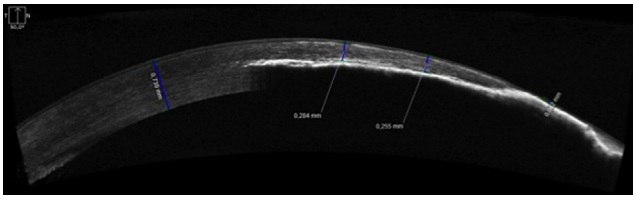

Figure 6. High-definition corneal OCT image with various measurements of corneal thickness (patient 3).

pigments known as BiochromaEyes® dedicated exclusively to corneal tattooing, with a neutral pH more closely approximating the physiologic pH of the cornea. It also appears advisable, in light of these observations, to limit the use of dyes when there is early corneal edema or when the endothelial cell density is near the threshold for decompensation, since hydration is the most significant factor favoring both oxidation and migration.

Above all, it would seem that the best way to prevent this unattractive and inflammatory phenomenon which is very disturbing to the patient, would be to use inks that do not contain iron oxide (for example, ink composed exclusively of carbon for the black pigment).

Conclusion

Corneal tattooing currently represents a simple, low-risk therapeutic alternative which may be proposed for numerous indications for aesthetic and functional reasons. However, to date, we have not possessed sufficient data to be sure of its effects over time. The possible color change over time which we report must be made aware to ophthalmologists and patients when they are choosing a treatment technique. Certain conditions such as early corneal edema in susceptible eyes must limit use of tattoo inks containing iron. Improvements should come from industry so as to make available pigments without iron oxide for corneal indications.

Disclosure of interest

The authors declare that they have no competing interest.

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