Histological observation of trabecular meshwork in a patient with Axenfeld-Rieger syndrome—a new theory for the mechanism of ectropion uvea in congenital glaucoma

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Dear Editor,

I am Dr. Satoru Kase, from the Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University. I write to present the case of clinicopathological findings in Axenfeld-Rieger syndrome (ARS). ARS is characterized by ophthalmic abnormalities arising in the trabecular meshwork (TM) and iris. ARS manifests various maldevelopmental abnormalities caused by involvement with neural crest cells. Early-onset glaucoma can take place in patients with ARS having iris abnormalities. Recent studies have shown that trabeculotomy/trabeculectomy played a crucial role in the management of intraocular pressure (IOP)[1]. In contrast, while histological findings of enucleated eyes with end-stage of ARS were documented[2], pathology of TM and iris obtained during trabeculectomy has yet to be elucidated. We herein report a case of ARS progressing uveal ectropion in a patient who received glaucoma surgeries including tube implant surgery, and the histological findings in the TM. An 11-year-old male exhibited corneal opacity in both eyes oculi uterque (OU) at birth in April, 2005. IOP was 24 mm Hg OD and 23 mm Hg OS. The horizontal corneal length was 11 mm OU. Slit-lamp examination demonstrated corneal stromal opacity consistent with Haab’s line, malformation of iris indicating uveal ectropion, and posterior embryotoxon. Chromosome analyses revealed pericentric inversion of p25 and the q14 at chromosome 6. The patient was diagnosed with ARS. Neither he nor his family had any such medical history. The patient underwent trabeculectomy OD (Figure 1A) and trabeculotomy OS (Figure 1D) in 2005. Since then, because IOP had not been favorably controlled, he underwent trabeculotomy OD twice and OS once from 2007 to 2013 (Figure 1B, 1E). He also received goniotomy in 2012. He further received Baerveldt tube implant surgeries combined with trabeculectomy twice OU from 2013 to 2014. In 2015, the best-corrected visual acuity was 12/20 OD and 3/20 OS. IOP was 21 mm Hg OD and 9 mm Hg OS, respectively. Slit-lamp examination revealed the Baerveldt tubes that were inserted into the anterior chamber as well as progression of uveal ectropion and atrophy of the iris OU (Figure 1C, 1F). He finally underwent the tube implant surgery plus trabeculectomy OD. During trabeculectomy, the angle tissue was obtained in the supranasal site where there were no previous surgeries. IOP currently remains 12 mm Hg OU with topical anti-glaucoma eye drops and oral acetazolamide. Goldman perimetry demonstrated inferior visual field defects consistent with glaucomatous nasal step. Institutional Review Board in Hokkaido University waived application for clinical researches of humans because this is a single case report. Informed consent was obtained to present the clinicopathological data of this patient in the international journal. This study adhered to the tenets of Declaration of Helsinki.

Histological Findings in the Angle Tissue

The TM tissues surgically excised were immediately fixed with 4% paraformaldehyde in an operating room. After the excised tumor tissues were embedded in paraffin, 5 μm thickness sections were made. The slides were dewaxed, rehydrated, and rinsed in phosphate-buffered saline twice for 10min. Slides were submitted for hematoxylin & eosin staining and immunohistochemistry. As a pretreatment in
immunohistochemistry, microwave-based antigen retrieval was conducted in 10 mmol/L citrate buffer (pH 6.0). These slides were immersed in 3% hydrogen peroxide, and then in normal goat serum for 10min and 30min, respectively. Sections were incubated with anti-thrombomodulin (dilution 1:25, Dako 1009, Japan) monoclonal antibody at a room temperature for 2h. Positive signals were visualized using 3-3’ diaminobenzidine as a substrate. Slides were examined using a Keyence BZ-9000 (Keyence, Osaka, Japan) microscope. Angle splitting did not occur and pseudo-angle was found far more anterior to the Schwalbe’s line (thick arrow in Figure 2A). Ciliary muscles (CM) dislocated anteriorly constituting the deformed angle (Figure 2A). TM and Schlemm’s canals (SC) were located posterior to the Schwalbe’s line (Figure 2A, square). TM became atrophic and did not connect to the anterior chamber (AC; Figure 2A). Descemet’s membrane-like structure (Figure 2A, thin arrow) was observed in the anterior surface of the iris. Positive reactions to thrombomodulin, a marker for vascular endothelial cells, were clearly observed in SC, where SC was almost collapsed (Figure 2B, arrow).

The ocular pathology of the trabecular tissues and peripheral iris, together with the enucleated eye with ARS, proved that neural crest cells ceased to develop late in gestation\(^3\). It has been demonstrated that angle recession took place on the TM around 28\(^{th}\) week of gestation\(^3\). In this case, histological findings of the angle tissue characteristically revealed incomplete angle recession and anterior dislocation of the CM. Although TM and a variety of thrombomodulin-positive SC seemed to have developed normally, the arrest of angle recession might have caused atrophy of TM and partial occlusion of SC because of no aqueous outflow.

This case further presented progression of uveal ectropion in both eyes (Figures 1), which was different from congenital ectropion with other ocular abnormalities\(^4\). Histologically, amorphous linear structure, consistent with Descemet’s membrane, elongated to the anterior iris (Figure 2A, thin arrow), suggesting iridocorneal endothelial syndrome (ICE)-like phenomenon. These data suggest that direct contact of corneal endothelium to the iris because of incomplete angle recession may be a primary cause of endothelial growth
and Descemet’s membrane formation on the iris surface. In addition to this, shrinkage of extended Descemet’s membrane-like structure on the iris surface may cause uveal ectropion as shown in the schematic illustration of uveal ectropion formation (Figure 3).

There may be other interpretations for acquired ectropion uvea, which may be caused by previous glaucoma surgeries and intraocular surgeries. Trabeculotomy[3] and trabeculectomy[4] were reported to cause growth of corneal endothelium over the surface of TM, which might create subsequent uveal ectropion. However, uveal ectropion had been observed prior to initial surgery in this case. Moreover, this patient has yet to receive other intraocular surgeries such as cataract and vitreoretinal surgeries and the vitreous incarceration has not been observed. Therefore, our case showed acquired progressive uveal ectropion underlying maldevelopment of angle recession and ICE-like phenomenon, which might repeatedly increase IOP.

The management of IOP in patients with ARS is challenging. Basically, medication is the first choice; however, most of the patients with ARS who developed early-onset glaucoma are likely to need to undergo glaucoma surgery. Recently, it has been reported that combined trabeculotomy/trabeculectomy is useful to regulate IOP in ARS patients with early-onset glaucoma by relative long-term follow-up[5]. The present case is unique because the early-onset glaucoma complicated iridociliary abnormality and progressive uveal ectropion. Since this patient required several glaucoma surgeries, early-onset glaucoma in ARS patients presenting with progressive uveal ectropion allows ophthalmologists to predict poor response to conventional trabeculotomy/trabeculectomy. According to the histological findings, trabeculotomy and goniotomy may have played critical roles in the reduction of IOP against the abnormality of angle recession and the later development of ICE-like phenomenon. Once the cornea is clear, 360 degrees suture trabeculotomy ab interno can be achieved with muscle rotations and two separate incisions into the eye[6]. If 360 degrees suture trabeculotomy ab interno is not proceeding well, one can change to conventional incisional goniotomy ab interno or trabeculotomy ab externo due to the abnormal position of Schlemm’s canal. In the case of ARS having uveal ectropion, it is reported that Baerbeldt implant surgery combined with trabeculectomy contribute to reconstruction of a novel outflow if IOP was not favorably controlled by trabeculotomy/trabeculectomy[1,2]. Previous glaucoma surgery or anti-glaucomatous therapy can affect TM specimens obtained during surgery. Therefore, there is a limitation in this study: the control sample would be obtained from other types of glaucoma for comparison of histopathology.

In conclusion, we first describe the mechanism of progressive ectropion uvea by showing the histology of angle in a case with ARS. It may be reasonable to choose goniotomy to prevent later development of ICE-like changes caused by maldevelopment of angle recession. Abnormality of angle splitting should be released by trabeculotomy or goniotomy, which may prevent or delay ICE-like changes and lead to promotion of intraocular fluid outflow and reduction of IOP. Tube implant surgeries combined with trabeculectomy are further required when patients with refractory ARS has progressive uveal ectropion.

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