

Pathological Study of Secondary Glaucoma due to Congenital Syphilis-A New Theory of Vasculitis in the Schlemm's Canal

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Abstract

Aims: To investigate histopathological changes in trabeculectomy (TLE) specimens in patients with secondary glaucoma due to congenital syphilis.

Methods: Eleven eyes of 8 patients were used. The areas of TLE observed by gonioscopy were photographed before the surgery. Each of 13 TLE specimens (two eyes received TLE twice) were processed for light and transmission electron microscopy.

Results: There was no inflammation in the anterior chamber at the time of TLE in any eyes. Gonioscopy showed a mixture of normal, thick pigmentation and peripheral anterior synechia. A variety of histological changes in the angle was observed among the samples or even in the same samples: normal (7 eyes) or occluded (8 eyes) Schlemm's canal with (7 eyes) or without (4 eyes) inflammatory cells. These various changes were also observed in TLE samples taken from the same angle appearance observed by gonioscopy. Inflammatory cells were restricted to the area around the Schlemm's canal and collector channels.

Conclusion: Persistence of super-long-term inflammation in the angle might be the reason for the late onset of secondary glaucoma due to congenital syphilis. Infiltration of inflammatory cells around the Schlemm's canal and collector channel despite no inflammation in the anterior chamber strongly suggested vasculitis of the Schlemm's canal and collector channels. A variety of histological changes in the angle might be primarily caused by segmental inflammation of these vessels.

Introduction

Congenital syphilis is caused by *Treponema pallidum* infection through the placenta in the embryonic stage and causes ophthalmic symptoms in childhood and adulthood. Ocular involvement of congenital syphilis consists of interstitial keratitis, anterior uveitis, acute iridocyclitis, chorioretinitis, perivasculitis, optic neuritis and secondary glaucoma. Interstitial keratitis and anterior uveitis usually occur between the ages of 5 and 20 years [1] but secondary glaucoma due to congenital syphilis occurs an extremely long time, 30 or 40 years, after interstitial keratitis [2-4]. Knox suggests that low-grade, subclinical recurrence of keratitis involves the trabeculae in the inflammatory process and produces a rapid rise in resistance to aqueous outflow [2]. Sugar supposes that trabecular space obstruction and pathologic alterations cause late glaucoma associated with interstitial keratitis [5] but the mode of obstruction in the angle has not yet been reported. We conducted a histopathological study of secondary glaucoma due to congenital syphilis to clarify the reason for increased intraocular pressure (IOP) using trabeculectomy (TLE) specimens.

Materials and Methods

Consecutive patients who underwent TLE with a diagnosis of secondary glaucoma due to congenital syphilis were enrolled in this study. The diagnosis of ocular congenital syphilis was made based on clinical history, characteristic clinical findings of post-interstitial keratitis (corneal neovascularization, stromal opacity), chorio-retinal atrophy (salt and pepper retinopathy), and blood examination results. The absence of acquired syphilis was confirmed by an interview and the clinical history. Slit lamp examination using gonioscopy and fundus examination using an ophthalmic scope after pupil dilatation was performed to make a diagnosis. Routine blood tests, including AIDS, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination (TPHA), were performed in all patients before TLE.

The patients completed a questionnaire before TLE as to whether they had experienced temporarily decreased vision or whether they had been told by their parents that they had complained of photophobia in childhood. All procedures in this study were conducted according to the Helsinki Declaration, and the ethics committee of the Japanese Red Cross Medical Center approved this study.

TLE specimens were immersed in a mixture of 2.5% formalin and 1% glutaraldehyde overnight, and dissected into three pieces (0.5x1.5 mm, 1.5x1.5 mm, 0.5x1.5 mm). Middle part of each specimen was processed for paraffin embedding to be used for hematoxylin-eosin and routine immunohistochemical staining of thrombomodulin to detect the Schlemm's canal [6,7] and collector channels, and that of CD68 to detect macrophages and monocytes. The other two pieces from each TLE specimen were processed for Epon embedding. Thin sections of Epon embedding were stained with toluidine blue and observed by light microscopy. Ultrathin sections were stained with uranium acetate and lead citrate, and observed by transmission electron microscopy (TEM).

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Results

Clinical features of 11 eyes of 8 patients (2 males and 6 females, mean age: 67 ± 8.2 years, range: 55-81 years) used in this study are listed in table 1. All eyes showed abnormalities in the corneal stroma; stromal opacity or neovascularization. Silt lamp examination could not detect inflammation in the anterior chamber in any eyes before TLE. Three different gonioscopic appearances were observed: normal, thick pigmentation over the surface of trabecular meshwork, and peripheral anterior synechia (PAS). PAS was observed in 7 eyes with a combination of thick pigmentation of the trabecular meshwork (Table 1). A cluster of round peripheral chorio-retinal atrophy was observed in all eyes, except for two eyes in which this abnormal finding was found only in the contralateral eye because the fundus of eyes with TLE was invisible due to corneal opacity and/or cataracts (Patients 4 and 8, Table 1). Five patients had episodes of temporary decreased vision before the age of 20, whereas three patients had not been aware of any ocular complaints before visiting our clinic. All patients showed positive RPR and TPHA on blood examination. Two eyes of two patients received TLE twice because IOP increased again to more than 21 mmHg after the first TLE. There was no episode of intraocular surgery in any eyes before the first TLE.

A variety of histological changes in the angle were observed among

the samples or even in the same samples (Table 2). The Schlemm's canal became occluded with (Figure 1b) or without inflammatory cells, and remained open with (Figure 2) or without inflammatory cells (Table 2). In the specimens with the occluded Schlemm's canal, the canal endothelium completely disappeared (Figure 1d) with CD68-positive cells (Figure 1a), or they remained discontinuously (Figure 1e). Two eyes of 2 patients (Patients 3 and 6) underwent TLE twice, and both eyes in each patient showed different changes in the Schlemm's canal. The Schlemm's canal was occluded in both eyes at the first TLE and opened in both eyes in the second TLE (Figures 3a, 3b, 4a and 4b). Macrophages, CD68-positive cells and lymphocytes (Figure 3c) were found around the Schlemm's canal at the first and second TLE in both the patients. Granuloma composed of epithelioid cells (Figure 4c) expressing subplasmalemmal linear densities (Figure 4d) was found in Patient 3. Trabecular cells in all epon and paraffin blocks with the occluded Schlemm's canal disappeared, and the trabecular beams seemed to fuse (Figure 3a). The trabecular cells and endothelium of the Schlemm's canal seemed to be normal at the first TLE where the Schlemm's canal was open (Figure 3c). Macrophages, CD68-positive cells and lymphocytes were also found around the collector channels (Figures 1a, 1c, 3d and 4e). These inflammatory cells were mostly restricted to the walls of collector channels and Schlemm's canal, and were not found in the stroma of the cornea or sclera. Basal

Patient no. and eye	Age, sex	IOP before TLE (mm Hg)	Angle*	Cornea	Fundus	Age at decreased vision
1 R	74, F	28	TP, PAS	SO and NV	CRA	7 years
1 L	74, F	23	TP, PAS	SO and NV	CRA	7 years
2 R	58, F	30	TP	SO	CRA	6 years
2 L	58, F	30	TP, PAS	SO	CRA	6 years
3 R	55, M	42	N, TP, PAS	NV	CRA	No decreased vision
4 L	61, F	28	TP, PAS	SO	CRA †	7 years
5 R	79, F	37	N, TP, PAS	NV	CRA	No decreased vision
5 L	79, F	50	N, TP, PAS	NV	CRA	No decreased vision
6 L	67, F	48	TP	SO	CRA	18 years
7 R	78, F	24	TP	NV	CRA	No decreased vision
8 R	68, M	60	TP	SO	CRA †	5 years

CRA: Chorio-Retinal Atrophy; GV: Ghost Vessels; OP: Intraocular Pressure; N: Normal appearance; NV: Neovascularization; PAS: Peripheral Anterior Synechia; SO: Stromal Opacity; TLE: Trabeculectomy; TP: Thick Pigmentation over the surface of trabecular meshwork

*Angle appearance observed by gonioscopy.

† CRA was found in the contralateral eye.

All patients except Patients 3, 5 and 7 experienced temporary decreased vision. Patients 3, 5 and 7 had no corneal opacity, but had neovascularization in the cornea

Table 1: Clinical characteristics of patients who underwent trabeculectomy.

Patient no. and eye	IFC at 1st TLE	IFC at 2nd TLE	Length of SC at 1st TLE*	Length of SC at 2nd TLE*
1 R	-		0-221 (10 o'clock, TP)	
1 L	-		251-317 (10 o'clock, PAS)	
2 R	-		236-251 (1 o'clock, TP)	
2 L	-		0 (1 o'clock, TP)	
3 R	+	+	53-86 (1 o'clock, PAS)	257-342 (10 o'clock, N)
4 L	+		0-74 (10 o'clock, TP)	
5 R	+		313-330 (11 o'clock, PAS)	
5 L	+		39-256 (11 o'clock, N)	
6 L	+	+	0-28 (12 o'clock, TP)	256-275 (3 o'clock, TP)
7 R	+		28-129 (12 o'clock, TP)	
8 R	+		0-78 (11 o'clock, TP)	

IFC: Inflammatory Cells in the angle; TLE: Trabeculectomy; Angle appearance observed by gonioscopy in the area of trabeculectomy; TP: Thick Pigmentation on the surface of trabecular meshwork; PAS: Peripheral Anterior Synechia; N: Normal

* Location of TLE and angle appearance by gonioscopy

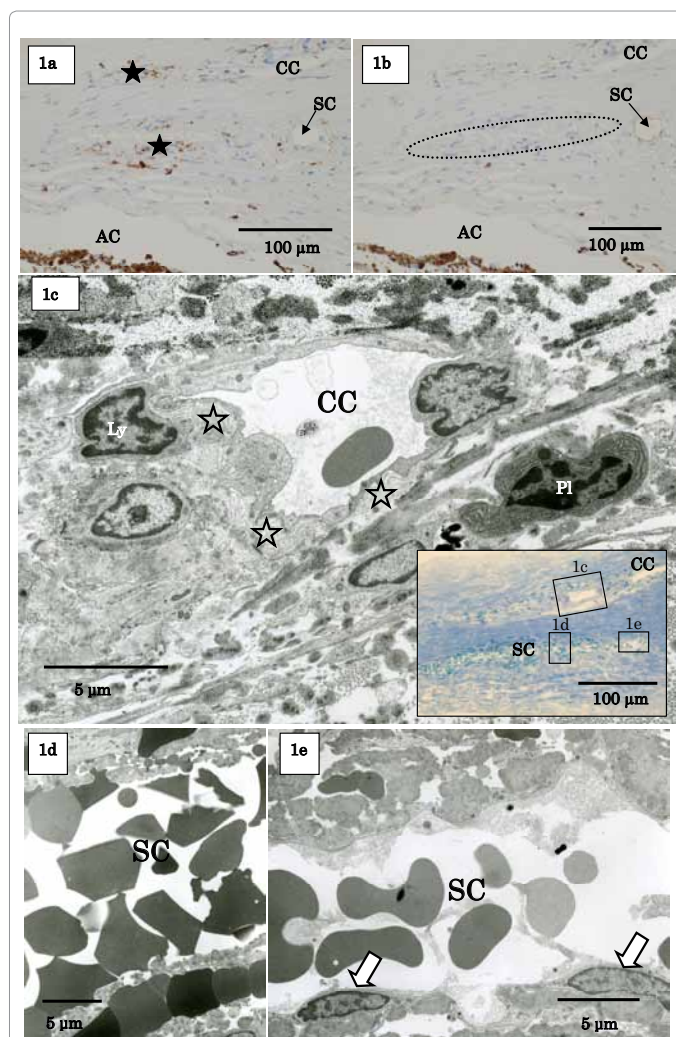
The periods between the first and the second TLE in Patients 3 and 6 were 9 months and 14 days, respectively.

Table 2: Histological results of trabeculectomy (TLE) specimens; existence of inflammatory cells (IFC) in the angle and the length of the Schlemm canal (SC).

lamina layering of the collector channels was often observed in the blocks which showed the occluded Schlemm's canal (Figure 1c). Cells containing melanin granules were found in the trabecular meshwork and around the Schlemm's canal (Figures 2a, 2b inset, 3b, 4a, 4b and 4c).

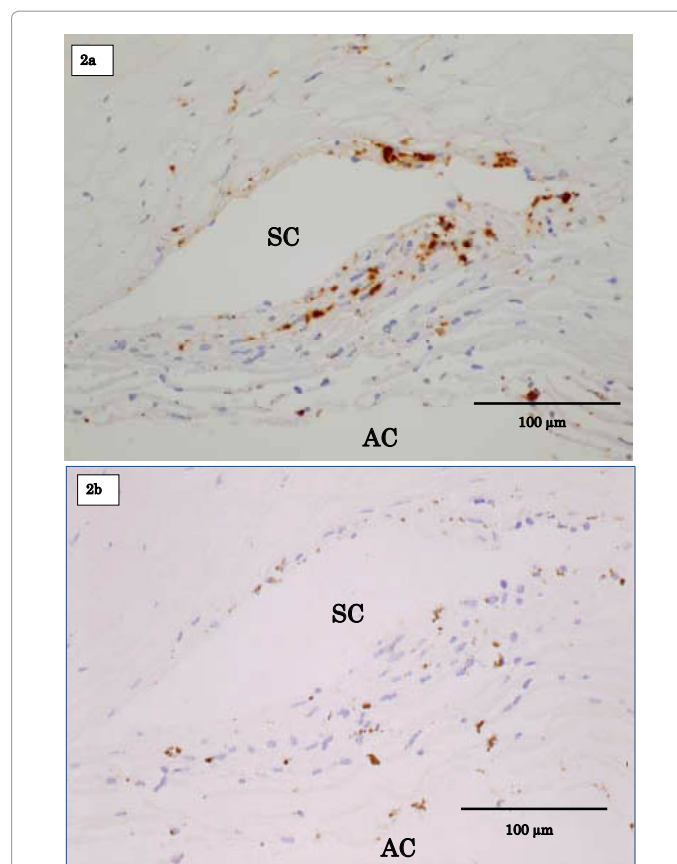
Discussion

Stromal opacity in the cornea, strong pigmentation over the surface of trabecular meshwork, PAS and chorio-retinal atrophy are well-known clinical features of congenital syphilis [1-5]. We believed



AC: Anterior Chamber

Figure 1: Light microscopy (1a-b, 1c inset) and transmission electron microscopy (1c-e) of the trabecular meshwork and Schlemm's canal (SC) in Patient 7. Photographs of paraffin embedding (1a, 1b) were taken from serial sections. 1c inset: light microscopy of Epon embedding. 1a: CD68-positive cells (asterisks) are seen at the collector channels (CC) and occluded area of the Schlemm's canal. Immunohistochemical staining of CD68. 1b: Immunohistochemical staining of thrombomodulin demonstrates positive staining of the endothelium of Schlemm's canal. The canal (SC) was occluded to 28 μ m in length. Dotted circle indicates supposed region of the canal. 1c: Boxed area in 1c inset. Infiltration of plasma cells (Pl) and lymphocytes (Ly) was observed around the collector channel (CC). Basal lamina layering (asterisks) was also seen in the collector channel. 1c inset: Bleeding is seen in the occluded area of Schlemm's canal. Toluidine blue stain. 1d and 1e: Boxed area in 1c inset. Endothelium of the canal disappeared in the middle part of Schlemm's canal (1d); but inner wall cells (arrows) remained in the posterior part of the canal (1e).



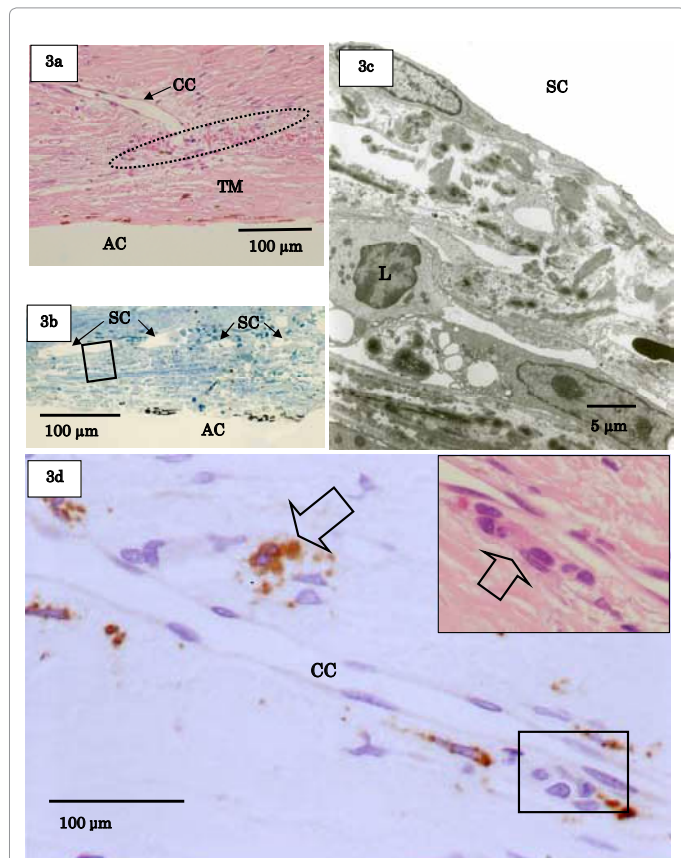
AC: Anterior Chamber

Figure 2: Light microscopy of immunohistochemical staining, CD68 (2a) and control staining (2b) in Patient 5 (right eye). TLE was performed in the area of peripheral anterior synechia. CD68-positive cells were found around the Schlemm's canal (SC), which was normally open. Although melanin-containing cells were seen, CD68-positive cells were negative in control staining.

that secondary glaucoma in all our patients might have been caused by syphilis infection because RPR and TPHA were all positive on the blood examination. In addition, they had typical features of syphilis infection in the cornea with stromal opacity or neovascularization in the angle with thick pigmentation over the surface of trabecular meshwork and in the fundus with chorio-retinal atrophy. An episode of temporarily decreased vision in childhood or in the first decade of life was observed in 5 patients; which strongly suggested the development of interstitial keratitis that might have been caused by congenital syphilis. It was interesting that the remaining three patients with no ocular episode had no corneal opacity, but had corneal neovascularization that might have been caused by keratitis. Therefore, keratitis without corneal opacity in childhood might have been overlooked by their parents. Neovascularization in acquired syphilitic keratitis is less common and less obvious than that associated with late congenital syphilis [8]. Although it may be difficult to strictly differentiate congenital and acquired syphilis clinically, our patients met the criteria for congenital syphilis of post-interstitial keratitis (corneal neovascularization, stromal opacity) and chorio-retinal atrophy (salt and pepper retinopathy). Although acquired syphilis could not be ruled out in the three patients without ocular episodes when young, the lack of ocular complaints before occurrence of secondary glaucoma, age at occurrence of secondary glaucoma and involvement of anterior segments including corneal neovascularization suggested that congenital syphilis

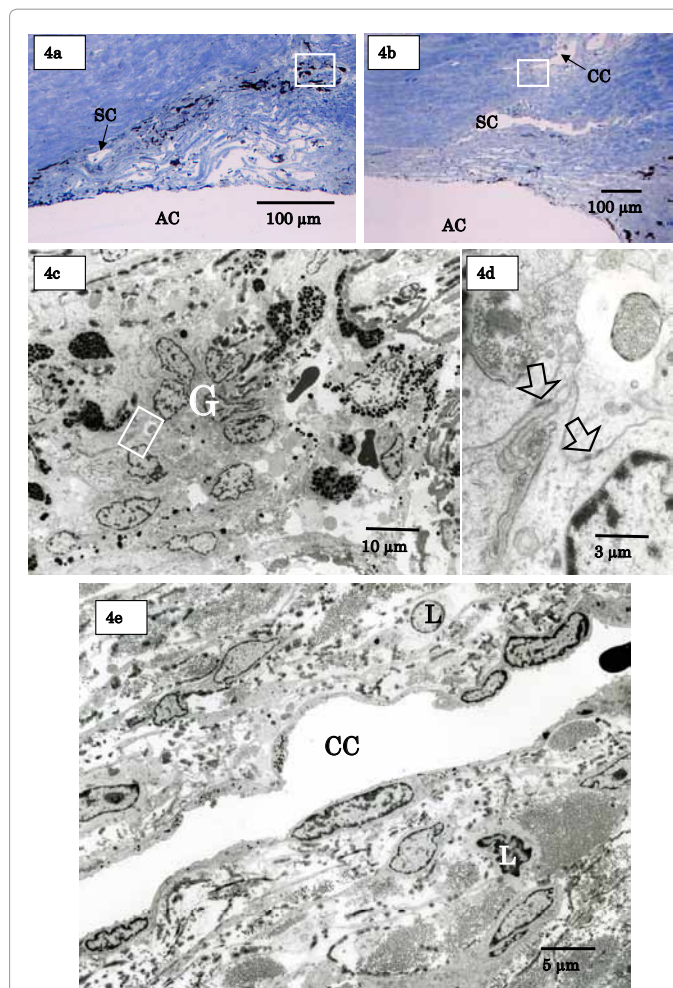
was more likely to be the reason for secondary glaucoma. It was somewhat surprising that there was infiltration of CD68-positive cells, macrophages and lymphocytes around the Schlemm's canal (Figures 1c, 2 and 4c) and collector channels (Figures 1a, 1c, 3d and 4e) despite no inflammation in the anterior chamber when observed by slit lamp examination. CD68-positive cells might have been mostly macrophages because monocytes were rarely observed on light microscopy of HE stain and TEM. Secondary glaucoma due to congenital syphilis occurs an extremely long time, 30 or 40 years, after interstitial keratitis [2,3]. As it is reported that inflammation in the angle in congenital syphilis may cause secondary glaucoma [2], our histological observation suggested that inflammation in the angle might persist for an extremely long period from the initial infection and destroy the outflow routes extremely slowly.

There were 8 eyes in which the length of Schlemm's canal was less than 150 μm . According to a previous study, the average length of Schlemm's canal in the human eye was $264 \pm 55 \mu\text{m}$ [9], and less than 150 μm may be regarded as narrowing or occlusion of the canal, which may be a serious risk for aqueous outflow and cause refractive glaucoma.



AC: Anterior Chamber; L: Lymphocyte

Figures 3: Light microscopy (3a, 3b, 3d) and transmission electron microscopy (TEM, 3c) of the trabecular meshwork (TM), Schlemm's canal (SC) and collector channel (CC) at the first (3a, 3d) and second (3b, 3c) TLE in Patient 6. 3c is TEM of the boxed area of 3b. 3a: The Schlemm's canal was almost occluded. Note the severely damaged trabecular meshwork with loss of trabecular cells and fusion of the trabecular beams. Hematoxylin-eosin (HE) stain. 3b: The Schlemm's canal was normally open. Toluidine blue staining. 3c: Trabecular cells and endothelium of the Schlemm's canal seemed to be normal. 3d: Immunohistochemical staining of CD68 detected positive cells along the collector channel (CC). Inset (HE stain) is a serial section of the boxed area of 3d. Cluster of epithelioid cells is seen (arrows in 3d and inset).



Figures 4: Light microscopy of the trabecular meshwork and Schlemm's canal (SC) at the first (4a) and second (4b) TLE of Patient 3. Toluidine blue staining. 4c, 4d: Transmission electron microscopy of granuloma (G) at the first TLE. 4e: Transmission electron microscopy of collector channel (CC) at the second TLE. 4a: The Schlemm's canal (SC) was almost occluded at the first TLE. Most of the trabecular cells disappeared. 4b: The Schlemm's canal was normally open at the second TLE. 4c: Ultrathin section of the boxed area in 4a. Granuloma (G) composed of epithelioid cells occupying the posterior part of the Schlemm's canal. 4d: Large magnification of boxed area in 4c. Epithelioid cells had subplasmalemmal linear densities (arrows). 4e: Ultrathin section of the boxed area in 4b. Lymphocytes (L) were observed along the collector channel (CC).

Occlusion of the canal in secondary glaucoma due to congenital syphilis may be caused by granuloma (Figure 4c) or macrophage infiltration (Figures 1a, 1d and 1e) around the canal. Syphilis infection causes granulomatous inflammation [10-12]. Although glaucoma composed of epithelioid cells was found only in one eye (Figure 4c) in our study, histological changes of the angle could be classified as granulomatous inflammation. It was also interesting that two trabeculectomy specimens from the same eyes revealed different results, showing the occluded and normally opened Schlemm's canal (Patients 3 and 6). Segmental variability of the trabecular meshwork in normal and glaucomatous eyes is proposed [13]. Primary open angle glaucoma eyes have the significantly smaller Schlemm's canal perimeter and inner wall length than normal eyes [9]. However, such a conspicuous difference in the trabecular meshwork and the Schlemm's canal observed between the samples of first and second TLE in those patients or even in the same samples (left eye of Patient 5) strongly suggested that the changes of

the angle were not uniform. If inflammation of the angle in congenital syphilis had been caused by anterior chamber inflammation (ie, iritis, anterior uveitis), the changes of the whole angle might have been uniform or similar. Further, if inflammation of the angle had arisen from contiguous inflammation of the iris root, histological changes of the angle with the same angle appearance by gonioscopy might have shown the same results. However, the actually occluded Schlemm's canal was observed with all types of angle appearance (Table 2). These results suggested that the changes in the Schlemm's canal might not be caused by anterior chamber inflammation or contiguous inflammation of the iris root. Although, the Schlemm's canal is easy to collapse near the collector channel in the experiment of artificially elevated IOP [14], the occlusion of the canal observed in our specimens seemed to occur through a different mechanism as discussed below.

The regional difference in the damage to the Schlemm's canal suggested that inflammation in the angle might descend from collector channels. It seemed clear that vasculitis in the outflow routes existed in our TLE specimens because inflammatory cells were found mostly around the collector channels and the Schlemm canal but not in the stroma of the cornea or sclera. In the embryonic stage, the blind end of the future Schlemm's canal extends deeply into the sclera and forms a unit of collector channels [15,16]. Three to four collector channels drain approximately 1 mm of the Schlemm's canal, forming a unit in an experiment of monkey eyes by Mercocox injection into the Schlemm's canal and collector channels [17]. If the inflammation of the limbal region in congenital syphilis descended via upstream of the deep scleral plexus, one unit of the collector channels and the Schlemm's canal would be involved and another unit might be affected differently. In addition, segmental involvement of inflammation in the collector channels and the canal might occur during the development of these vessels. Segmental validity observed in our study might be explained by the above speculation. There have been reports concerning vasculitis in acquired and congenital syphilis [18-21]. Leucocytoclastic vasculitis of post-capillary venules in papulopurpuric lesions of the dermis is reported in congenital syphilis [20]. Small vessels in the eye might also be involved and the cluster of shaped chorio-retinal atrophy in our patients also suggested segmental vasculitis in choriocapillaries, which showed a lobular pattern. The Schlemm's canal and collector channels are suggested to be of blood vessel origin [15]. Recently, we had confirmed that E-selectin and PECAM-1 were present in the endothelium of Schlemm's canal and collector channels [7]. E-selectin is involved in the slow rolling and stabilization of leucocytes on the endothelium during inflammation [22]. PECAM-1 is crucial for leukocyte transmigration through the intercellular junction vascular endothelium cells; [23] and therefore, the infiltration of inflammatory cells around the Schlemm's canal and the collector channels suggested the existence of "Schlemm's canalitis" in congenital syphilis. The evidence for macrophages and lymphocytes around the Schlemm's canal and collector channels in our TLE samples strongly suggested vasculitis as part of the granulomatous microangiopathy, which was also observed in secondary glaucoma due to sarcoidosis [24]. Basal lamina layering in the collector channels (Figure 1c) also supported the notion of the long persistence of microangiopathy [25].

In summary, histological examination of TLE specimens from secondary glaucoma due to congenital syphilis revealed the infiltration of macrophages and lymphocytes around the Schlemm's canal and collector channels despite no inflammation in the anterior chamber. These findings strongly suggested the extremely long persistence of vasculitis in the Schlemm's canal and collector channels. Further investigation might be needed to identify how the Schlemm's canal or

collector channels were involved in other types of inflammation in the anterior segment of the eye.

Ethics Approval

This study was approved by ethics committee of Japanese Red Cross Medical Center.

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Contributors

SH: performed pathological examination, wrote this manuscript. TH: performed trabeculectomy, pathological examination, wrote this manuscript and supervised this study. TT: performed pathological examination.

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