


Case Report

A Case Report of Secondary Glaucoma in a Patient with HTLV-1: Discussion about the Management of Secondary Glaucoma Due to Recurrent Granulomatous Uveitis

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Abstract: Purpose: to investigate secondary glaucoma resulting from uveitis in a patient infected with Human T-cell Leukemia Virus Type 1 (HTLV-1) pathologically and discuss the management of glaucoma with recurrent uveitis. Clinical course: An octogenarian woman diagnosed as a carrier of HTLV-1 experienced recurrent uveitis and a sudden rise in intraocular pressure (IOP) in both eyes. Due to the uncontrolled IOP and severely damaged visual field in her left eye, a combined procedure of trabeculectomy and DGIS (glaucoma drainage implant surgery, Baerveldt 350) was performed. The presence of HTLV-1 provirus was detected in the aqueous humor. Her trabeculectomy sample was processed for light microscopic observation. Following an irregular follow-up, she presented with a sudden decrease in vision and pain in her fellow eye, four years after the glaucoma surgeries. Her right eye exhibited a significant accumulation of mutton-fat-like keratic precipitates. Results: Clinical manifestations revealed the presence of granulomatous uveitis. The combined glaucoma surgery, along with continuous topical corticosteroid medication post-surgery in her left eye, effectively suppressed the high IOP spikes and the recurrence of uveitis for 4 years. The pathological examination of the outflow pathways showed a range of damages in Schlemm's canal (SC), including SC endothelial loss, narrowing, and occlusion, as well as loss of trabecular meshwork (TM) cells and fused TM beams. Conclusion: Combined GDIS and trabeculectomy represents a promising approach for managing such refractory cases of secondary glaucoma. Continuous topical corticosteroid medication is strongly recommended to prevent irreversible changes in SC and TM associated with granulomatous uveitis.

Keywords: HTLV-1; secondary glaucoma; uveitis; glaucoma drainage implant



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1. Introduction

Among the category of systemic viral infectious diseases, human T-cell leukemia virus type 1 (HTLV-1) is acknowledged as the causative virus of uveitis [1–4]. Cross-sectional investigations conducted in Japan have uncovered a prevalence of uveitis associated with HTLV-1, reaching 112.2 cases per 100,000 individuals carrying HTLV-1 [5]. The primary ocular manifestations observed in HTLV-1 patients comprise visual impairment characterized by haziness, the presence of floating specks in the visual field (VF), vision blurring, ocular hyperemia, ocular discomfort, and sensitivity to light [6]. The principal clinicopathological features of HTLV-1-associated uveitis encompass opacification of the vitreous and inflammation of the retinal blood vessels [7]. Secondary glaucoma was not documented in individuals afflicted with HTLV-1 [8], nor was visual impairment attributed to glaucoma in association with HTLV-1 as a frequently reported occurrence [6]. To the best of our knowledge, there exists no pathological analysis elucidating the outflow pathways

responsible for secondary glaucoma in HTLV-1 patients. In the present study, we aim to ascertain the underlying cause of secondary glaucoma in an HTLV-1 patient via examination of trabeculectomy (TRAB) specimens and to discuss the management of recurrent uveitis-associated secondary glaucoma.

2. Case Report

The study protocols were duly approved by the Institutional Review Board of the Japanese Red Cross Medical Center. An octogenarian woman experienced recurrent uveitis in both eyes and encountered elevated intraocular pressure (IOP) reaching up to 28 mmHg since October 2016. The patient had been diagnosed as an HTLV-1 carrier since 1999 and was found to have coexisting Graves' disease since 2002. On the initial visit to our medical facility, the IOP in her left eye soared to 56 mmHg despite the administration of maximum glaucoma medication. The angle was open with a tent-like PAS in both eyes (Figure 1a). The Cup/Disc ratio was 0.8 in the right and 0.95 in the left eye. Although her left visual field suffered severe damage with stage V in Aulhorn–Greve's classification and 32 μ m in average thickness of the optic nerve cube in OCT ($R = 68 \mu$ m), effective IOP control was achieved following combined GDIS (glaucoma drainage implant surgery, Figure 1b) and trabeculectomy (TRAB) performed on 10 January 2019, in conjunction with thrice-daily topical steroid medication. Proviral DNA of human T-cell leukemia virus type 1 (HTLV-1) was detected via polymerase chain reaction (PCR) testing in the aqueous humor during the aforementioned surgeries. In the period encompassing March 2020 to May 2023, when examinations were not conducted at our medical facility, the patient underwent continuous monitoring under the care of a former ophthalmologist, as indicated in Table 1. Notably, topical corticosteroids were not prescribed for the right eye during this interval; rather, only glaucoma medication was administered. Subsequently, on 24 April 2023, the patient sought consultation, describing an abrupt onset of visual impairment and discomfort in the right eye. Despite the use of topical glaucoma medications, her right eye exhibited an elevated IOP of 32 mmHg. Profuse mutton-fat-like keratic precipitates (KP) obstructed the posterior segment of the eye, indicating possible vitritis due to her strong complaints of floaters in the right eye. Immediate interventions consisted of a 40 mg triamcinolone retrobulbar injection and topical steroid application six times daily, in addition to the glaucoma medication. Within one month of initiating treatment, the IOP in her right eye decreased to less than 18 mmHg. With the resolution of KP (Figure 1b), the observation of tent-like peripheral anterior synechia (PAS, Figure 1b) and the discernment of her moderately damaged optic nerve head became feasible. Recurrent uveitis in both eyes had been ongoing since 1993. At the initial and subsequent visits, the levels of angiotensin-converting enzyme and soluble IL2 were measured, yielding values of 17.3 (18 February 2019) and 13.6 (22 May 2023) as well as 334 (18 February 2019) and 224 (22 May 2023), respectively. Sarcoidosis and other potential causes of uveitis were possibly ruled out through blood tests and chest X-ray examination. The corneal endothelial counts were 2746 and 2884/mm² (7 January 2019) and 2792 and 2751/mm² (2 March 2020) in the right and left eye, respectively. The conclusive visit transpired on 22 January 2024. Absence of inflammation was noted in both the anterior chamber and posterior segment of the eyes, with the application of topical glaucoma and three-times-daily corticosteroid medication in each eye. IOP and visual acuity (VA) measured 15 and 13 and 0.6 with correction and finger counting, respectively, in the right and left eyes. A comprehensive account of IOP and VA throughout the course is presented in Table 1. Notably, the visual field in the left eye exhibited a gradual exacerbation throughout the aforementioned period despite good IOP control (Figure 1c).

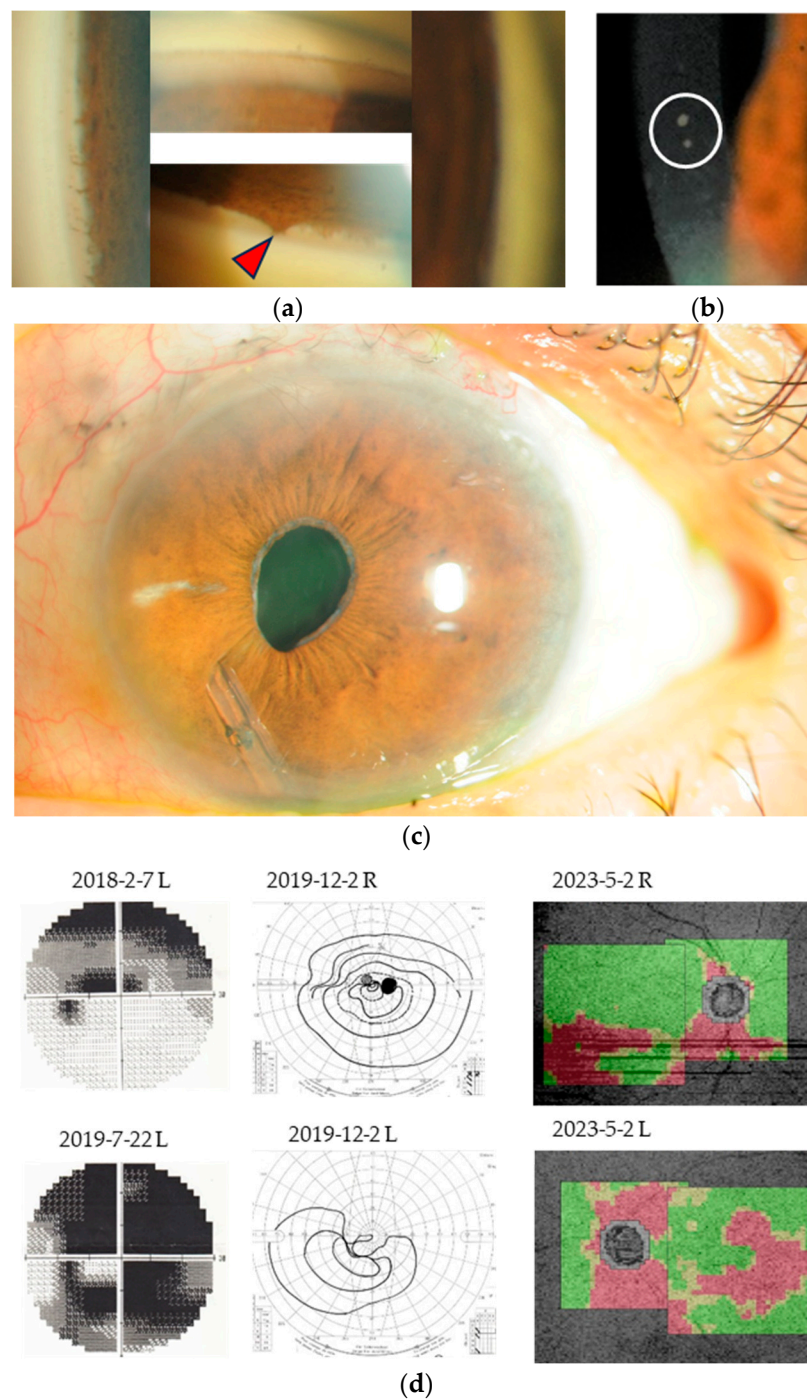
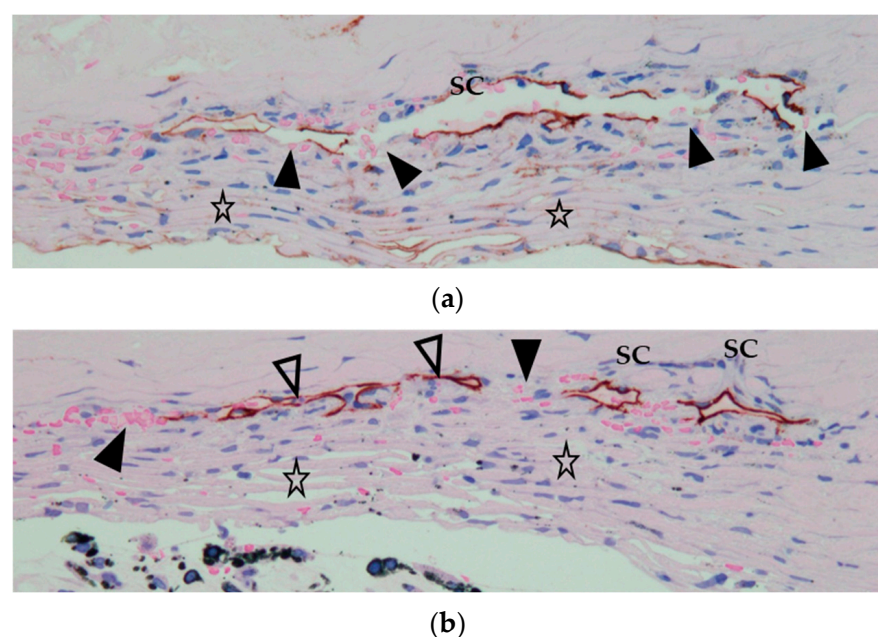


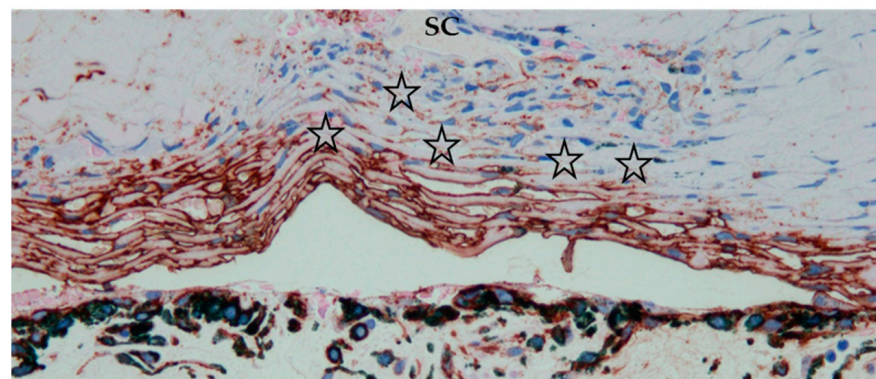
Figure 1. (a): Gonioscopic observations reveal the presence of tent-like peripheral anterior synechia (red arrowhead) at the 12 o'clock position in the right eye but normal angle in the other parts. (b): As illustrated in the image of the slit lamp photograph, a significant reduction in the abundance of keratic precipitates (KPs) was observed, with only two KPs remaining (circled), within a two-week period following the initiation of steroid medication. (c) Slit lamp image capturing the left eye featuring the glaucoma drainage implant (Baerveldt 350). The tube is inserted from the 6 o'clock position in order to locate as much as far from corneal endothelium. Although, tube was in contact with the iris, no inflammation in the anterior chamber was observed for more than 4 years. (d) The outcomes of visual field (VF) examinations and the optic disc's presentation in optic coherence tomography (OCT) were investigated. Over the duration of the study, a progressive deterioration in VF of the left eye was observed. Concurrently, a substantial decline in OCT was evident in both eyes, aligning with characteristic alterations associated with glaucoma.

Table 1. Visual acuity (VA) and intraocular pressure (IOP) during the course. CF: counting finger; HM: hand motion.

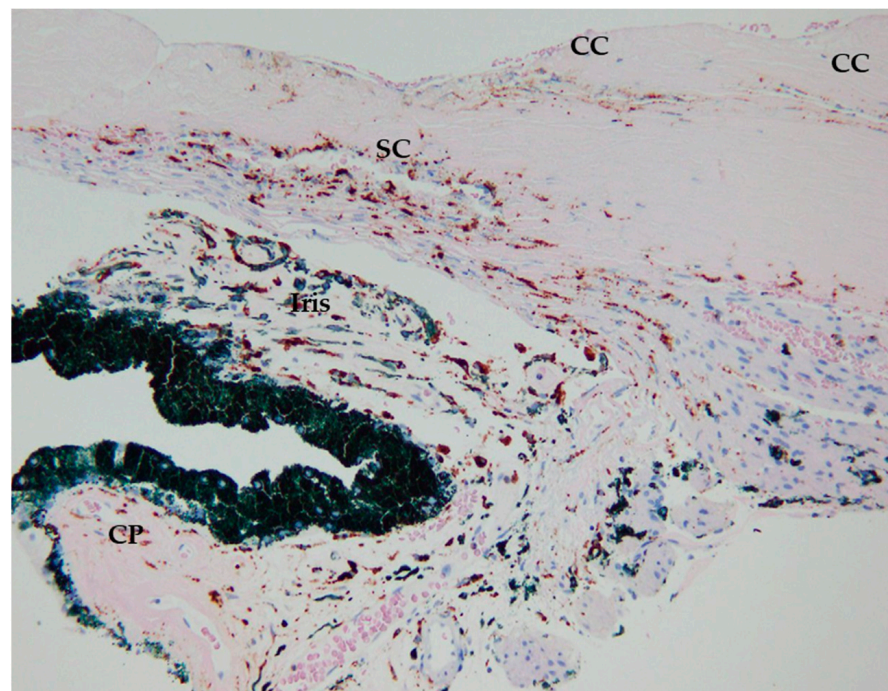
	VA (R)	VA (L)	IOP (R)	IOP (L)
7 January 2019	1.0	30 cm CF	23	56
18 March 2019	1.2	0.01	17	12
29 July 2019	0.9	0.01	14	9
2 December 2019	0.9	0.01	14	12
2 March 2020	0.9	20 cm CF	21	14
24 April 2023	/	/	32	12
8 May 2023	0.5	20 cm CF	10	8
26 June 2023	0.6	HM	16	14
14 July 2023	0.8	HM	10	8
22 January 2024	0.6	HM	15	13

The TRAB specimen obtained in January 2019 was promptly fixed using a mixture of 1% glutaraldehyde and 2.5% formalin, then divided into three blocks, embedded in paraffin, and processed for hematoxylin-eosin staining, as well as immunohistochemical staining of CD4, CD8, CD34, CD68, thrombomodulin, and podoplanin. Schlemm's canal (SC) displayed patency with localized absence of SC endothelium (SCE) (Figure 2a, black arrowheads), partial narrowing (Figure 2b, open arrowheads), partial obstruction (Figure 2b, black arrowheads), or total obstruction (Figure 2c). The trabecular meshwork cells were diminished in number (stars in Figure 2a,b), while the trabecular beams in the juxta-canalicular tissue (JCT) and corneoscleral meshwork fused together without any open spaces (stars in Figure 2c). CD68-positive cells were observed around SC, the collector channel (CC), ciliary muscle (CM), ciliary body, and iris (Figure 2d). Conversely, the anterior segment did not exhibit positive staining for CD4 and CD8 (Figure 3a,b), in contrast to the tonsils of HTLV-1-infected patients (Figure 3a,b inset). Prior to the implementation of glaucoma drainage implant surgery (GDIS) and TRAB surgery, informed consent was obtained for the utilization of pathological findings derived from TRAB specimens.

**Figure 2.** Cont.



(c)



(d)

Figure 2. (a–d) Light microscopic photographs capturing the details of the Schlemm's canal (SC) and trabecular meshwork (TM) under light microscopy, bar: 50 μ m: (a) Immunohistochemical staining of thrombomodulin in block No. 2; (b) immunohistochemical staining of CD34 in block No. 1; (c) immunohistochemical staining of podoplanin in block No. 3; (d) immunohistochemical staining of CD68 in block No. 2. The Schlemm's canal (SC) exhibited complete openness and appeared histologically normal (a). However, the SC endothelium locally showed signs of disappearance (indicated by black arrowheads in (a); additionally, certain regions within the trabecular meshwork (TM) displayed localized absence of TM cells (stars in (a,b)) in block No. 2. Furthermore, the SC experienced narrowing (indicated by open arrowheads in (b)) or complete collapse (solid arrowheads in (b)). The SC underwent complete collapse (c), while the corneoscleral and juxta-canalicular meshwork fused together, displaying sparse podoplanin staining (indicated by stars in (c)). In this region, a reduced number of TM cells were observed, and there were no spaces available for the aqueous humor. CD68-positive cells (d) were observed in the trabecular meshwork (TM), Schlemm's canal (SC), ciliary muscle (CM), ciliary processes (CP), and iris. These CD68-positive cells appeared to be infiltrated around the SC and collector channels (CC).

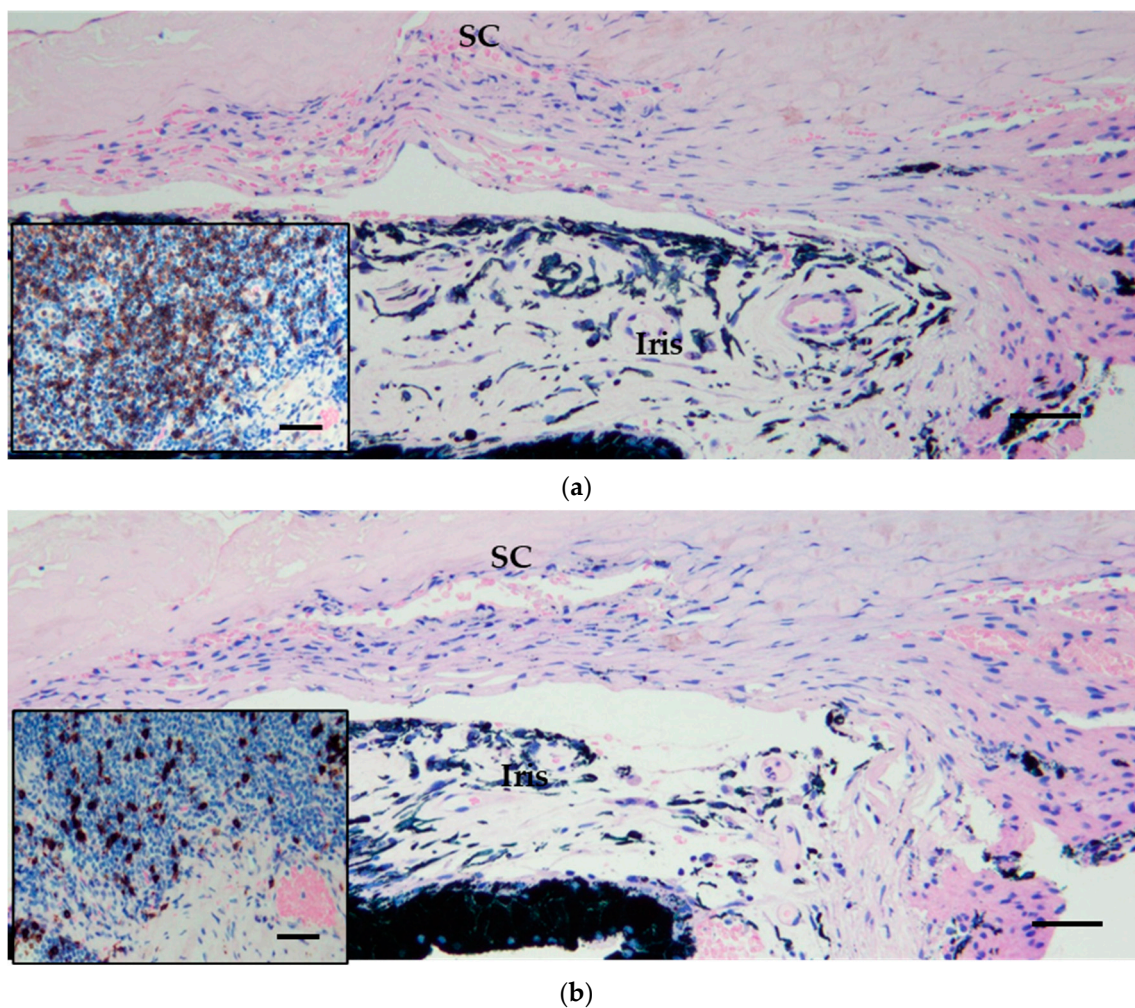


Figure 3. (a,b) A light microscopic image of the Schlemm's canal (SC), trabecular meshwork (TM), iris, and ciliary muscle (CM) is presented in the immunohistochemical staining of CD4 (a) and CD8 (b) in block No. 3 and No. 2, respectively (bar: 50 μ m). No CD4-positive cells (a) or CD8-positive cells (b) were detected in the anterior segment of the eye. Light microscopic images of a formalin-fixed tonsil specimen from a patient with HTLV-1 are presented in the immunohistochemical staining of CD4 (inset (a)) and CD8 (inset (b)) (bar: 50 μ m). Abundant CD4-positive cells and CD8-positive cells were observed.

3. Discussion

While numerous surgical techniques exist for the treatment of glaucoma, the combined GDI with TRAB procedure emerges as a highly viable choice for addressing refractory uveitis cases. This recommendation is particularly pertinent in instances where the intraocular pressure (IOP) in the left eye is markedly elevated and the visual field has suffered severe impairment [9]. The pathological alterations observed in the outflow pathways of the patient's left eye included the loss of TM cells, fusion of TM beams in the juxta-canalicular tissue (JCT) and corneoscleral meshwork, local disappearance of SCE (Figure 2c), and narrowing and collapse of SC (Figure 2b,c). The underlying cause of uncontrolled IOP in the left eye was evidently attributed to irreversible changes, such as fused TM and occluded SC (Figure 2c), in addition to the presence of CD68-positive cells in the JCT (Figure 2d). The previous literature reports histological evidence of granulomatous inflammation in the lungs of HTLV-1 patients [10]. Granulomatous or non-granulomatous uveitis has been documented in Japanese patients with HTLV-1 [2]. Although no granuloma was histologically observed in our patient's outflow pathways, clinical findings of mutton-fat-like KP (Figure 1b inset) and tent-like PAS (Figure 1b) were indicative of granulomatous uveitis. The

ACE reference range spans from 8.3 U/L to 21.4 U/L. It holds significance for assessment in suspected cases, as its elevation is indicative of sarcoidosis. The IL-2 reference range is observed to be between 145 U/L and 519 U/L. Given its elevated levels in conditions such as HTLV-1 infection, malignant lymphoma, and autoimmune diseases, its measurement proves valuable when suspicion arises. The patient's ocular clinical presentations in both eyes, along with a positive HTLV-1 PCR test and the findings from blood and chest X-ray evaluations, collectively indicated that the possibility of uveitis originating from a cause other than HTLV-1 is improbable. The absence of CD4- (Figure 3a) and CD8-positive cells (Figure 3b) in the anterior segment, despite HTLV-1-positive PCR in the aqueous humor, may be attributed to a negative reaction in immuno-histochemical staining caused by the glutaraldehyde present in the fixative used for the TRAB specimen. The presence of CD68-positive cells around SC and CC (Figure 2d) strongly suggests "microangiopathy in the outflow pathways" [11].

The lower incidence of secondary glaucoma in HTLV-1 patients [1] may be attributed to a lesser extent to granuloma formation compared to those with sarcoidosis [11]. Therefore, uveitis induced by HTLV-1 appears to have a lower likelihood of developing secondary glaucoma, unless there exists an underlying primary open-angle glaucoma (POAG) background [9]. The remaining inflammation inadequately controlled due to early termination of topical steroid therapy may have caused further damage to her optic nerve. Terada et al. documented that the majority of individuals afflicted with HTLV-1 uveitis exhibited a favorable visual prognosis. However, within a subset of seven patients (constituting 5.2%), experiencing visual impairment worse than 0.1 (logMAR = 0.1), glaucoma was found in three patients [6]. Hence, the elevation of intraocular pressure (IOP) among HTLV-1 patients should not be disregarded, and utmost caution ought to be exercised to safeguard against the development of secondary glaucoma in individuals diagnosed with uveitis. It is challenging to determine whether the abnormalities observed in the outflow pathways in POAG played a role in our patient's condition. The TM cell loss (Figure 2a,b stars) is likely responsible for the fusion of TM in the JCT and corneoscleral meshwork (Figure 2c stars). Recurrent infiltration of CD68-positive cells may have contributed to the loss of TM cells. We have previously demonstrated irreversible SC occlusion in cases of granulomatous inflammation due to sarcoidosis or secondary glaucoma resulting from congenital syphilis infection [11]. SC occlusion is a severe form of damage that leads to a refractory type of glaucoma [11]. Therefore, the prevention of SC occlusion and TM fusion is of utmost importance in cases of recurrent granulomatous inflammation in eyes with a history of elevated IOP or glaucomatous optic nerve damage. Following combined GDIS and TRAB surgery, which are not for the treatment of uveitis itself, along with continuous topical corticosteroid administration in the left eye, there was no recurrence of iritis and IOP elevation. We have previously proposed the use of topical steroid medication at least three times after GDIS in cases of secondary glaucoma caused by granulomatous inflammation [9]. While three-times-daily topical steroid medication may not completely suppress anterior segment inflammation or vitritis, it can help prevent recurrent IOP elevation [9,11]. A single administration of retrobulbar injection containing triamcinolone (40 mg) may suffice for the management of recurrent inflammation in the posterior segment. Continuous topical steroid instillation is strongly recommended for the patient's right eye. If the right eye develops steroid-induced glaucoma, GDIS should be considered since eyes that have undergone GDIS are protected against steroid-induced glaucoma [9].

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Institutional Review Board Statement: All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (The institutional Review Board and the Ethics Japanese Red Cross Medical Center) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was reviewed and approved by Japanese Red Cross Medical Center's Clinical Research Ethics Review Board, approval number 1564.

Informed Consent Statement: Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Data Availability Statement: All data generated or analyzed during this study are included in this published article and supporting images. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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