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?

Teruhiko Hamanaka * , Kenta Ashikaga , Mayumi Hosogai , Takao Tanaka , Shintaro Nakao , Toshinari Funaki

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A Case Report of Secondary Glaucoma in A Patient with HTLV-1

Discussion about the Management of Secondary Glaucoma Due to Recurrent Granulomatous Uveitis?

Kenta Ashikaga [a], Teruhiko Hamanaka [a,*], Mayumi Hosogai [b], Takao Tanaka [c], Shintaro Nakao [d] and Toshinari Funaki [a]

[a] Department of Ophthalmology, Japanese Red Cross Medical Center
[b] Department of Ophthalmology, Gunma University
[c] Ebisu Eye Clinic
[d] Department of Ophthalmology, Juntendo University, School of Medicine
* Correspondence: hamanaka.teruhiko@gmail.co.jp

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. The continuous topical corticosteroid medication is strongly recommended to prevent irreversible changes in SC and TM associated with granulomatous uveitis.

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1. Introduction

Among the category of systemic viral infectious diseases, human T-lymphotropic 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, 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]. Nevertheless, within a cohort of 78 patients affected by uveitis of uncertain etiology or nature, glaucoma attributed to HTLV-1 infection was absent in 32 cases (41.0%) of HTLV-1 positive individuals [8]. Only one documented instance of glaucoma in an HTLV-1 positive patient has been reported thus far [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 aimed to ascertain the underlying cause of

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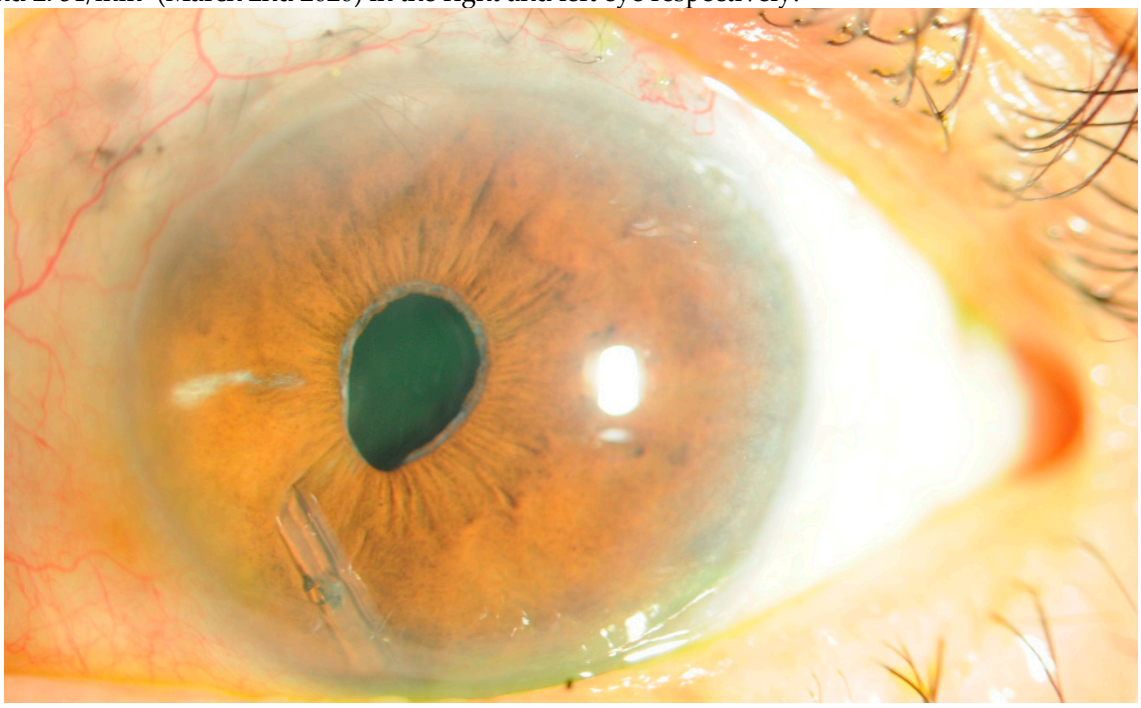
secondary glaucoma in an HTLV-1 patient via examination of trabeculectomy (TRAB) specimens, and to discuss the management of recurrent uveitis-associated secondary glaucoma.

2. Case Report

An octogenarian woman experienced recurrent uveitis in both eyes and encountered elevated intraocular pressure (IOP) reaching up to 28 mmHg since October 2016. 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. Although her left visual field suffered severe damage with stage V in Aurhorn-Graeve's classification and 46 μm in average thickness of optic nerve cube in OCT (R=69 μm), effective IOP control was achieved following combined GDIS (Fig. 1a) and trabeculectomy (TRAB) performed on January 10th, 2019, in conjunction with thrice-daily topical steroid medication. Proviral DNA of human T-lymphotropic virus type 1 (HTLV-1) was detected via polymerase chain reaction (PCR) testing in the aqueous humor during the aforementioned surgeries. After a period of irregular follow-up, she presented herself in April 2023, reporting sudden visual loss and pain in her 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 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 (Fig. 1b), the observation of tent-like peripheral anterior synechia (PAS, Fig. 1b), and the discernment of her moderately damaged optic nerve head became feasible. The patient had been diagnosed as an HTLV-1 carrier since 1999 and was found to have coexisting Graves' disease since 2002. 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 (February 18th, 2019) and 13.6 (May 22nd, 2023), as well as 334 (February 18th, 2019) and 224 (May 22nd, 2023), respectively. Sarcoidosis and other potential causes of uveitis were ruled out through blood tests and chest X-ray examination. The corneal endothelial counts were 2746 and 2884 /mm^2 (January 7th, 2019) and 2792 and 2751/mm^2 (March 2nd 2020) in the right and left eye respectively.



(a)

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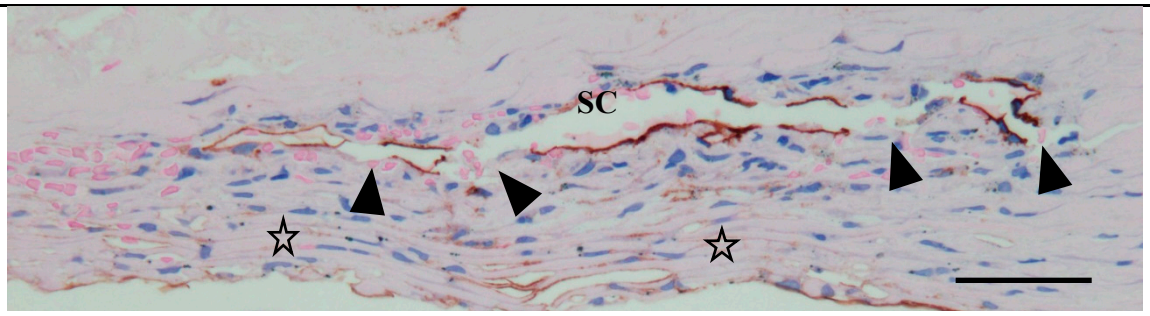
(**b**)

Figure 1. a, b a: Slit lamp image capturing the left eye featuring the glaucoma drainage implant (Baerveldt 350). The tubing is inserted from the 6 o'clock position in order to locate as much as far from corneal endothelium. Although, tube was contacting to the iris, no inflammation in the anterior chamber was observed for more than 4 years. b: Gonioscopic observations reveal the presence of peripheral anterior synechia at the 12 o'clock position in the right eye. As illustrated in the supplementary image of the slit lamp photograph, a significant reduction in the abundance of keratic precipitates (KPs) was observed, with only two KPs remaining (circled, inset), within a two-week period following the initiation of steroid medication.

The TRAB specimen 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) (Fig. 2a, black arrowheads), partial narrowing (Fig. 2b, open arrowheads), partial obstruction (Fig. 2b, black arrowheads), or total obstruction (Fig. 2c). The trabecular meshwork cells were diminished in number (stars in Fig. 2a, b), while the trabecular beams in the juxta-canalicular tissue (JCT) and corneoscleral meshwork fused together without any open spaces (stars in Fig. 2c). CD68-positive cells were observed around SC, the collector channel (CC), ciliary muscle (CM), ciliary body, and iris (Fig. 2d). Conversely, the anterior segment did not exhibit positive staining for CD4 and CD8 (Fig. 3a, b), in contrast to the tonsils of HTLV-1-infected patients (Fig. 3a inset, 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. The study protocols were duly approved by the Institutional Review Board of the Japanese Red Cross Medical Center.



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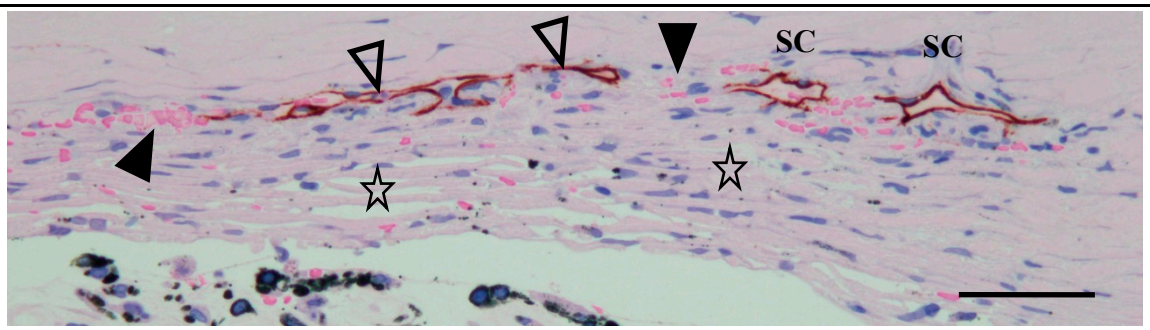

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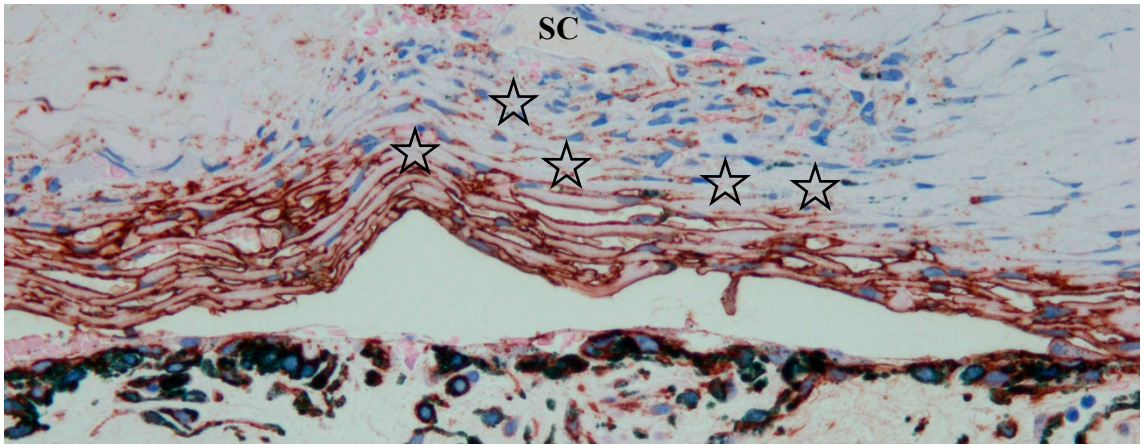

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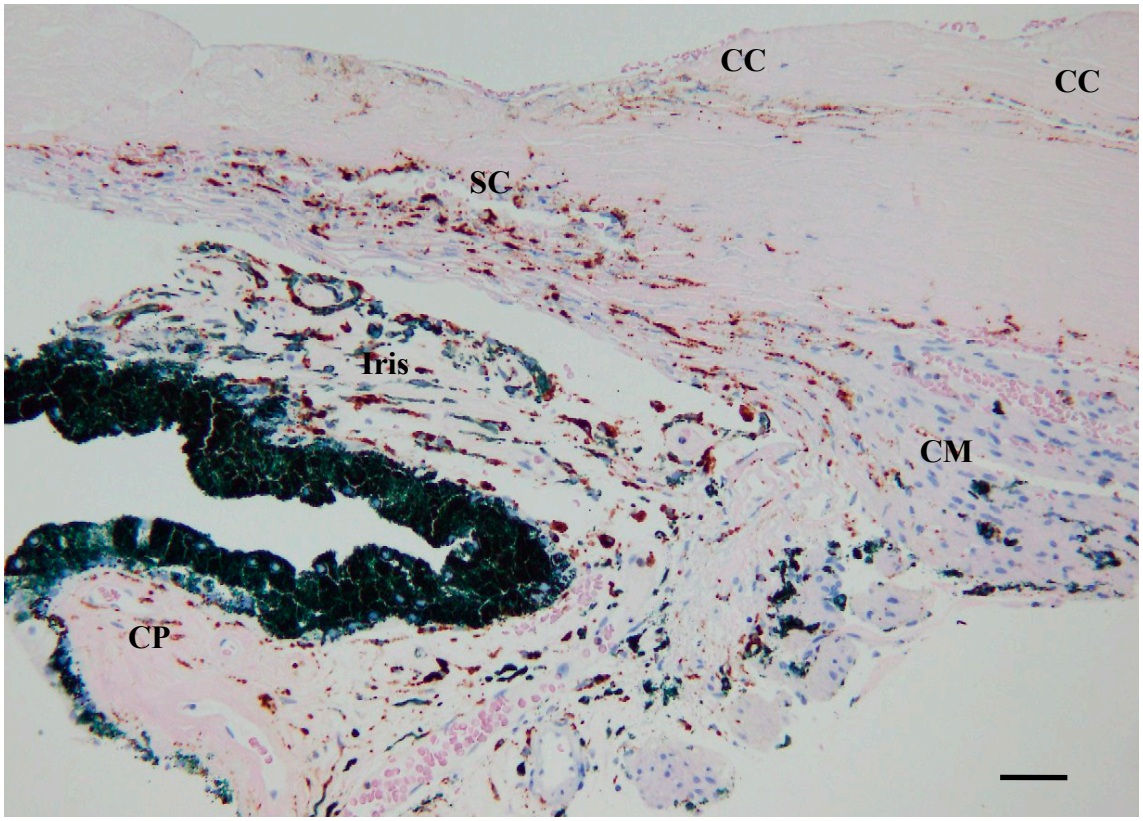

(d)

Figure 2. a-d **a-d**: A photomicrograph capturing the details of the Schlemm's canal (SC) and trabecular meshwork (TM) under light microscopy. bar: 50 μm **a**: immunohistochemical staining of

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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).

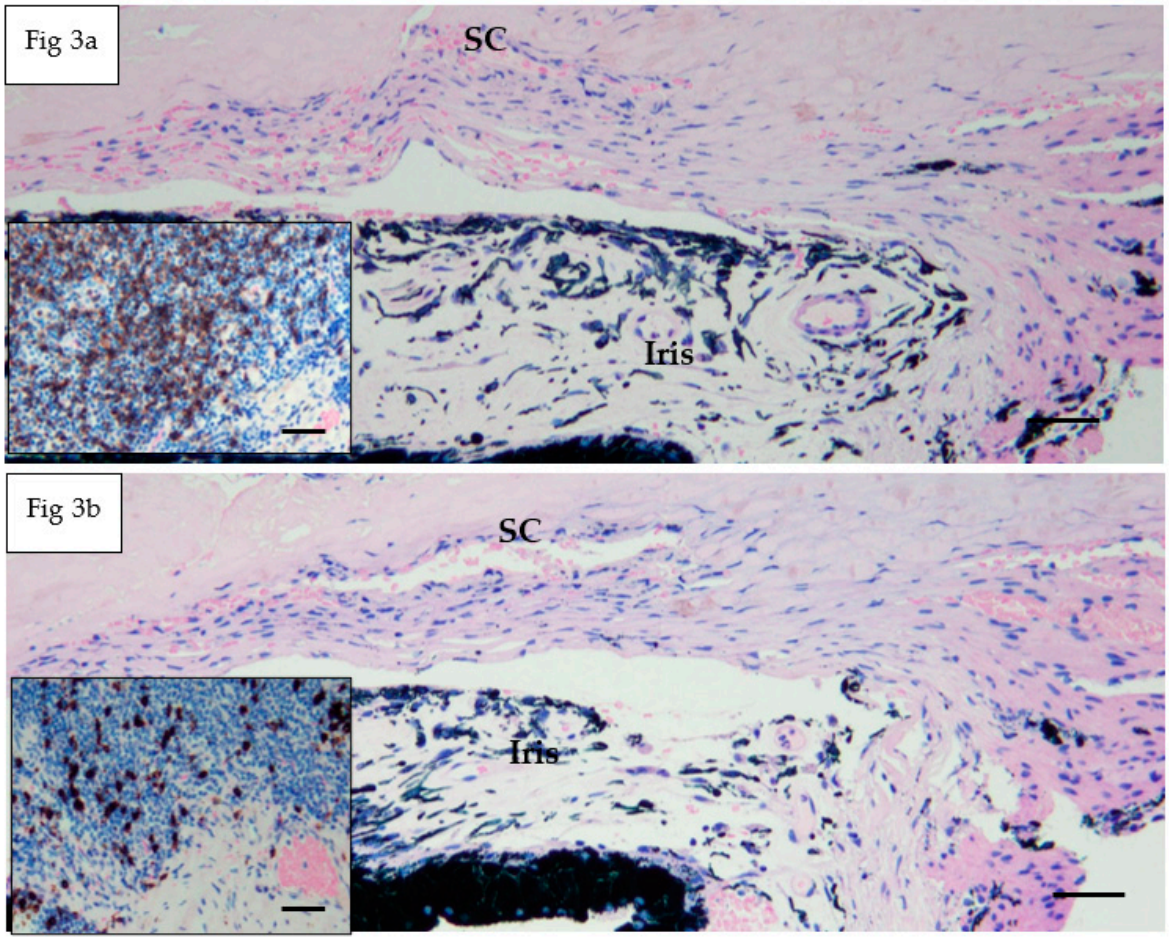

Figure 3. a, **b** A light microscopic image of the Schlemm's canal (SC), trabecular meshwork (TM), iris, and ciliary muscle (CM) is presented in the immunohistochemical staining of CD4 (a) and CD8 (b) in block No. 3 and No. 2, respectively (bar: 50 μm). No CD4-positive cells (a) or CD8-positive cells (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 μm). 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 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

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elevated and the visual field has suffered severe impairment. [12, 13] The pathological alterations observed in the outflow pathways of the patient's left eye included loss of TM cells, fusion of TM beams in the juxta-canalicular tissue (JCT) and corneoscleral meshwork, local disappearance of SCE (Fig. 2c), narrowing and collapse of SC. (Fig 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 (Fig. 2c), in addition to the presence of CD68-positive cells in the JCT (Fig. 2d). Previous literature reported histological evidence of granulomatous inflammation in the lungs of HTLV-1 patients [9]. 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 (Fig. 1b inset) and tent-like PAS (Fig. 1b) were indicative of granulomatous uveitis. 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 (Fig. 3a) and CD8 (Fig. 3b) positive cells 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 (Fig. 2d) strongly suggested "microangiopathy in the outflow pathways" [10].

The lower incidence of secondary glaucoma in HTLV-1 patients [1] may be attributed to a lesser extent of granuloma formation compared to those with sarcoidosis [2, 10, 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 [12]. Terada et al. documented that the majority of individuals afflicted with HTLV-1 uveitis exhibited a favorable visual prognosis. However, within a subset of 7 patients (constituting 5.2%), experiencing visual impairment worse than 0.1 (logMAR=0.1), glaucoma (42.9%) was determined as the causal factor [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 [14] played a role in our patient's condition. The TM cell loss (Fig. 2a, b stars) is likely responsible for the fusion of TM in the JCT and corneoscleral meshwork (Fig. 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 [11] or secondary glaucoma resulting from congenital syphilis infection [15]. SC occlusion is a severe form of damage that leads to a refractory type of glaucoma [11, 12, 14]. 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, 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 [12]. While three times daily topical steroid medication may not completely suppress anterior segment inflammation or vitritis, it can help prevent recurrent IOP elevation [12]. 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 [12].

Author Contributions: Kenta Ashikaga: acquisition of data and writing original draft; Teruhiko Hamanaka: pathological analysis, investigation, and writing – original draft preparation; Mayumi Hosogai: acquisition of data, supervision, and analysis; Takao Tanaka: review of the manuscript; Shintaro Nakao: supervision and review; Toshinari, Funaki: supervision and review. All authors made significant contributions to the work reported.

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Statement of ethics: 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.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 Statement: All authors have no conflicting interests to disclose.

References

1. Ohba, N.; Matsumoto, M.; Sameshima, M.; Kabayama, Y.; Nakao, K.; Unoki, K.; Uehara, F.; Kawano, K.; Maruyama, I.; Osame, M. Ocular manifestations in patients infected with human T-lymphotropic virus type I. Jpn. J. Ophthalmol. 1989, 33, 1–12.
2. Nakao, K.; Matsumoto, M.; Ohba, N. Seroprevalence of antibodies to HTLV-I in patients with ocular disorders. Br. J. Ophthalmol. 1991, 75, 76–78. [CrossRef]
3. Mochizuki, M.; Watanabe, T.; Yamaguchi, K.; Takatsuki, K.; Yoshimura, K.; Shirao, M.; Nakashima, S.; Mori, S.; Araki, S.; Miyata, N. HTLV-I uveitis: A distinct clinical entity caused by HTLV-I. Jpn. J. Cancer Res. 1992, 83, 236–239. [CrossRef] [PubMed] 4
4. Mochizuki, M.; Yamaguchi, K.; Takatsuki, K.; Watanabe, T.; Mori, S.; Tajima, K. HTLV-I and uveitis. Lancet 1992, 339, 1110.
5. Ikeda, E.; Ono, A.; Hikita, N.; Arima, K.; Mochizuki, M.; Yamaguchi, K.; Tajima, K.; Kiyokawa, H. Estimated Prevalence Rate of HTLV-I Uveitis in Chikugo. J. Jpn. Ophthalmol. Soc. 1998, 102, 327–332.
6. Terada, Y.; Kamoi, K.; Komizo, T.; Miyata, K.; Mochizuki, M. Human T Cell Leukemia Virus Type 1 and Eye Diseases. J. Ocul. Pharmacol. Ther. 2017, 33, 216–223. [CrossRef]
7. Kamoi, K.; Mochizuki, M. Human T-Cell Leukemia Virus Type 1. In Emerging Infectious Uveitis; Chee, S.-P., Khairallah, M., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp. 143–148.
8. Nakao, K.; Ohba, N. Clinical features of HTLV-I associated uveitis. Br. J. Ophthalmol. 1993, 77, 274–279. [CrossRef]
9. Sabiha Shahnaz, David Reich, Diana Arévalo-Valencia, Slavka Kucinska, Joanna Tulczynska, Jean Fleischman HTLV-1-Associated Adult T Cell Leukemia Lymphoma Presenting as Granulomatous Pneumocystis Jiroveci Pneumonia (PJP) and Hypercalcemia J Gen Intern Med. 2007 Mar; 22(3): 420–423. doi: 10.1007/s11606-006-0047-6 PMCID: PMC1824742
10. Hamanaka T, Akabane N, Sakurai T, Ikushima S.; Kumasaka T, Takemura T. Microangiopathy in Ocular Sarcoidosis Using Fluorescein Gonio and Fundus Angiography from Diagnostic and Therapeutic Aspects. Diagnostics 2021, 11, 39. https:// doi.org/10.3390/diagnostics11010039
11. Hamanaka T, Takei A, Takemura T, Oritsu M. Pathological study of cases with secondary open-angle glaucoma due to sarcoidosis. Am J Ophthalmol 2002; 134:17-26
12. Watanabe S, Hamanaka T, Sakurai T, Kobayashi K, Ishida N, Ebihara N. Evaluation of the outcome of long-tube shunt implant surgery in uveitic glaucoma patients by analyzing the background of uveitis. Int Ophthalmol, https://doi.org/10.1007/s10792-020-01601-3
13. Hamanaka T, Otora K, Ono K, Ishida N. Long-term results of non-valved Glaucoma drainage implant surgery and glaucoma drainage implant combined with trabeculectomy. Indian J Ophthalmol. 2014 Sep; 62(9): 911–916. doi: 10.4103/0301-4738.PMC4244735
14. Hamanaka, T,. Sakurai, T,. Fuse N,. Ishida, N., Kumasaka, T., Masaki Tanito, M., Comparisons of Schlemm's canal and trabecular meshwork morphologies between juvenile and primary open angle glaucoma Exp. Eye Res. 2021 https://doi.org/10.1016/j.exer.2021.10871
15. Hayashi S, Hamanaka T, Takemura T. Pathological Study of Secondary Glaucoma due to Congenital Syphilis-A New Theory of Vasculitis in the Schlemm's Canal. J Clinic & Experiment Ophthalmol 2012, 3:249. doi:10.4172/2155-9570.1000249J http://dx.doi.org/10.4172/2155-9570.1000249