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ORIGINAL PAPER

Clinical features of anterior uveitis caused by three different herpes viruses

Jun-ichi Sakai · Yoshihiko Usui · Jun Suzuki · Takeshi Kezuka · Hiroshi Goto

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Abstract

Purpose To compare the clinical findings in patients with anterior uveitis (AU) caused by herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV).

Methods We retrospectively analyzed the clinical profiles of HSV-AU (14 patients), VZV sine herpete (ZSH-AU: 21 patients), and CMV-AU (17 patients) diagnosed by the detection of corresponding viral DNA in aqueous humor samples by polymerase chain reaction. Further, five patients with Posner–Schlossman (P–S) syndrome were selected as controls for CMV-AU.

Results Patients with CMV-AU were predominately male or older in age, and all cases were unilateral except for three patients with CMV-AU. Mutton-fat keratic precipitates (KPs) were found mostly in patients with HSV-AU and ZSH-AU. Severities of AU and viral load were the highest in ZSH-AU, followed by HSV-AU and CMV-AU. Iris atrophy was observed in HSV-AU (50%) and ZSH-AU (76%), with typical morphology of round type and sector type, respectively. In patients with CMV-AU, a ring-shaped KP was found in 53% patients, 76% of whom showed a decreased number of corneal endothelial cells. CMV was not detected in the aqueous humor of patients with typical P–S syndrome.

Conclusion Clinical findings of HSV-AU and VZV-AU were similar; however, more inflammatory findings were observed in VZV-AU. Iris atrophy morphologically differed in HSV-AU and VZV-AU. Inflammatory findings in CMV-AU were mild, and clinical features of iritis differed from those of the two former groups. A difference in the etiology between CMV-AU and P–S syndrome was observed.

Keywords Anterior uveitis · Corneal endotheliitis · Cytomegalovirus · Herpes simplex virus · Varicella zoster virus

Introduction

Herpetic anterior uveitis (AU) is a well-recognized intraocular inflammatory disease that accounts for

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J. Sakai · Y. Usui (✉) · J. Suzuki · T. Kezuka · H. Goto
Department of Ophthalmology, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
e-mail: usuyoshi@gmail.com

3–7% of all uveitis cases in Japan [1–3]. It is the major cause of infectious AU, with herpes simplex virus (HSV) [4] and varicella zoster virus (VZV) [5, 6] identified as the most common causative agents by molecular techniques. Common clinical manifestations of AU include acute unilateral iridocyclitis, iris atrophy, elevation of intraocular pressure (IOP), and keratic precipitates (KPs), usually the mutton-fat type [7, 8]. HSV-AU and VZV-AU cases reportedly have good visual prognosis unless complicated by secondary glaucoma and corneal involvement [9].

Cytomegalovirus (CMV) has been recently identified as a causative agent of AU and corneal endotheliitis [10, 11]. The virus has been detected in patients with AU not caused by HSV or VZV and in some patients with presumed Posner–Schlossman (P–S) syndrome or Fuchs heterochromic iridocyclitis [12, 13]. A distinct feature of CMV-AU is coin-shaped KPs and corneal endothelial cell (CEC) dysfunction [14, 15]. CMV infection in AU patients has been reported to reduce the number of CECs leading to bullous keratopathy [16]. Although the pathogenetic mechanism of CMV-AU remains unknown, it is believed to involve direct CMV infection of the CEC, because owl's eye-like morphology was observed by confocal microscopy [17, 18].

In patients with HSV iritis without keratitis and VZV iritis without skin eruption (zoster sine herpete) [19, 20], the diagnosis of herpetic uveitis can be difficult. Furthermore, CMV-AU is often misdiagnosed as P–S syndrome. For the management of infectious uveitis, identification of the characteristic findings for early diagnosis and treatment is crucial to avoid irreversible ocular tissue damage. In this study, we investigated the clinical manifestations of uveitis caused by three different herpes viruses and attempted to clarify the distinctive features of each type of AU. We explored the pathogenesis of HSV-AU and VZV-AU by investigating inflammation severity and prevalence of iris atrophy according to viral load and iris vasculature on indocyanine green angiography (ICGA). Moreover, we examined the difference between CMV-AU and P–S syndrome on the basis of clinical findings.

Materials and methods

Overall, 52 patients (55 eyes) with HVS-AU, VZV sine herpete (ZSH-AU), or CMV-AU diagnosed by the detection of corresponding viral DNA in aqueous humor samples by polymerase chain reaction (PCR), who attended the uveitis clinic of Tokyo Medical University Hospital, Japan, in 2001–2014, were included in this retrospective review. The study was approved by the Tokyo Medical University institutional review board, and informed consent was obtained from all participants included in the study.

Following suspected herpetic AU based on clinical findings, such as unilateral involvement, the presence of KP, and elevated IOP, aqueous humor samples were collected for viral DNA detection by PCR. Fourteen patients with HSV-AU, 21 patients with VZV sine herpete (ZSH-AU), and 17 patients with CMV-AU were included in this study, all with a confirmed diagnosis based on the detection of respective viral DNA by PCR. We selected consecutive patients with AU caused by HSV, VZV, and CMV. Of the patients with P–S syndrome who visited our hospital, we selected five who consented to anterior chamber puncture during the study period. Patients with dendritic keratitis and herpes zoster were excluded because the diagnosis was usually made clinically and PCR was not always performed. Quantitative PCR was performed for ten patients with HSV-AU, 15 patients with ZSH-AU, and 15 patients with CMV-AU [21]. None of the patients received anti-viral therapy before sample collection for PCR examination. In patients with bilateral disease, the more severely affected eye was selected for examination. Aqueous humor samples of five male patients with P–S syndrome who provided consent for the examination (anterior chamber puncture) were also tested for PCR examination as a control group. Diagnosis of P–S syndrome was based on clinical manifestation, including unilateral open-angle glaucoma with recurrent mild anterior chamber (AC) inflammation, the presence of some fine non-pigmented KPs on the central or inferior cornea, depigmentation in the trabecular area, and no anterior or posterior synechiae [22–24].

An ophthalmologic examination was performed when required based on the patients symptoms and included measurement of the best-corrected visual acuity, slit-lamp biomicroscopy, tonometry, and indirect ophthalmoscopy in all patients. Uveitis activity

was assessed using the SUN criteria, as described previously [25]. Recurrence was assessed by the findings of iritis or corneal endotheliitis. Specular microscopy was performed for seven patients with HSV-AU, 13 patients with ZSH-AU, and 17 patients with CMV-AU. A CEC number under 1500/mm or 40% lower than the fellow eye was defined as CEC loss. Between patients with HSV-AU and ZSH-AU, we compared the severity of iritis using the number of inflammatory findings, such as ciliary injection, Descemet's membrane folds, corneal endotheliitis, mutton-fat KPs, iris atrophy, pupil distortion, and grading of AC cells (1+–3+). An inflammation score was thereby generated (each finding was assigned 1 point; range 0–9; Fig. 1).

In five patients with ZSH-AU, ICGA was performed using a confocal scanning laser ophthalmoscope (F-10, Nidek, Gamagori, Japan). Clinical manifestations during the course of disease were compared on the basis of the causative herpes virus.

Statistical analysis

Statistical analysis was performed using SPSS ver. 22, and the statistical significance was set at $p < 0.05$. One-way analysis of variance (ANOVA) was used to compare the mean age of the three patient groups, and Scheffe's F test was performed as a post hoc test when ANOVA yielded a significant difference. Chi-square test and Fisher's exact test were used where appropriate to compare the demographic and clinical characteristics of the three groups. Residual analysis was performed to identify the specific difference when Chi-square test yielded a significant difference among the three groups. Mann–Whitney U test was used to compare the severity between HSV-AU and ZSH-AU.

Results

Demographic characteristics of the three patient groups

The mean follow-up period for HSV-AU, ZSH-AU, and CMV-AU cases were 24.1, 18.3, and 30.2 months, respectively. Before diagnosis, one patient with HSV-AU, one patient with ZSH-AU, and two patients with CMV-AU received cataract surgery. One patient with HSV-AU received cataract surgery and vitrectomy for retinal detachment, and one patient with CMV-AU received trabeculectomy and cataract surgery. The patients' demographic and clinical characteristics are summarized in Table 1. The mean age at presentation was significantly different among the three groups (HSV-AU, ZSH-AU, and CMV-AU: 50.5, 51.1, and 70.0 years, $p = 0.0003$, ANOVA), with a higher mean age in the CMV-AU group than that in the HSV-AU and ZSH-AU groups ($p < 0.01$ in both, Scheffe's F test). The gender ratio was significantly different among the three groups (HSV-AU, ZSH-AU, and

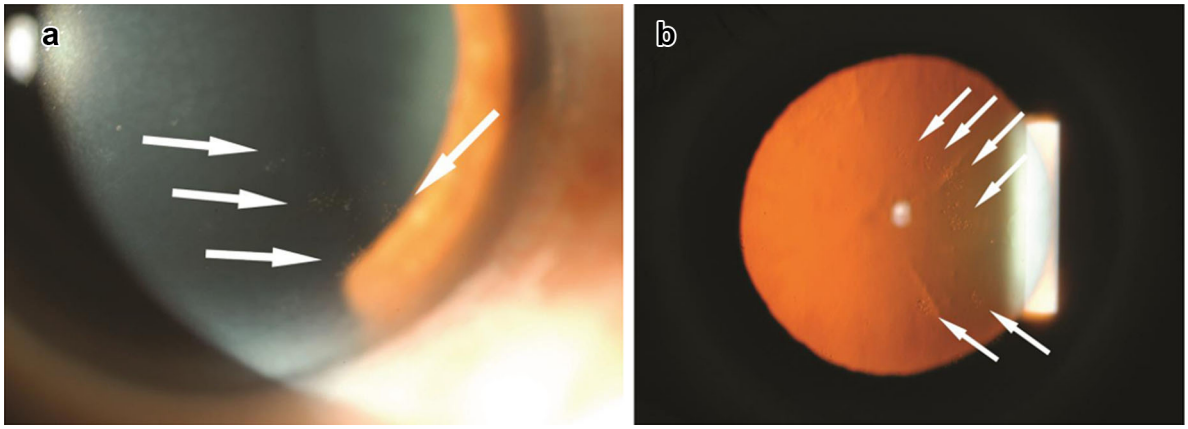

Fig. 1 Inflammation score in herpes simplex virus anterior uveitis (HSV-AU) and varicella zoster virus anterior uveitis (ZSH-AU) patients. The number of inflammatory findings, including ciliary injection, Descemet's membrane fold, corneal endotheliitis, mutton-fat keratic precipitates, iris atrophy, pupil distortion, and cells in the anterior chamber (grading 1+ to 3+), between HSV-AU and ZSH-AU patients are compared. The average number is indicated by a horizontal black line. *$p = 0.022$, Mann–Whitney U test

Table 1 Demographic and clinical background of the 52 patients studied

	HSV-AU (n = 14)	ZSH-AU (n = 21)	CMV-AU (n = 17)	p value
Age; mean ± SD (years)	50.5 ± 16.0	51.1 ± 16.8	70.0 ± 10.8[a]	< 0.01[b]
Sex, n (%)				< 0.01[c]
Male	5 (36)	6 (29)	13 (76)**	
Female	9 (64)	15 (71)*	4 (24)	
Eye involvement				< 0.05[c]
Unilateral	14 (100)	21 (100)	14 (82)	
Bilateral	0 (0)	0 (0)	3 (18)**	
Visual acuity				0.25[c]
≥ 20/20	7 (50)	5 (25)	4 (24)	
20/40–20/25	4 (29)	6 (27)	3 (18)	
≤ 20/50	3 (21)	10 (48)	10 (58)	
IOP elevation	12 (86)	21 (100)	17 (100)	0.06[c]
Recurrence	8 (57)	10 (48)	17 (100)**	< 0.01[c]

Data are expressed as number of patients with percent in parenthesis, unless indicated otherwise

HSV-AU herpes simplex virus anterior uveitis, *ZSH-AU* varicella zoster virus sine herpete, *CMV-AU* cytomegalovirus anterior uveitis, *IOP* intraocular pressure

*$p < 0.05$, residual analysis; **$p < 0.01$, residual analysis

[a]$p < 0.01$ versus HSV-AU and ZSH-AU, Scheffe's F test

[b]ANOVA

[c]χ^2 test

CMV-AU: M/F 5/9, 6/15, and 13/4, $p = 0.009$, Chi-square test); patients with CMV-AU were predominately male ($p < 0.01$, residual analysis). The prevalence of unilateral or bilateral disease was significantly different among the three groups ($p = 0.038$, Chi-square test). All patients with HSV-AU and ZSH-AU had unilateral involvement, while three patients with CMV-AU had bilateral disease ($p < 0.01$, residual analysis). Visual acuity at initial visit was diverse. Almost all patients in all three groups had elevated IOP (HSV-AU, ZSH-AU, and CMV-AU: 86%, 100%, and 100%, respectively). The recurrence rate was significantly different among the three groups ($p = 0.0018$, Chi-square test); it was the highest in the CMV-AU group (100%; $p < 0.01$, residual analysis) and approximately 50% in the HSV-AU and ZSH-AU groups. In patients with CMV-AU, seven (41%) were followed with a presumptive diagnosis of P–S syndrome and eight (47%) were followed with recurrent iritis and IOP elevation before being referred to our hospital.

Clinical features of corneal involvement

Either mutton-fat or fine non-granulomatous KPs were observed in all patients, but the predominant morphology differed among the patients in the three groups ($p = 0.00007$, Chi-square test; Table 2). Mutton-fat KPs were observed in many patients with HSV-AU (93%; $p < 0.05$, residual analysis) and ZSH-AU (86%; $p < 0.05$, residual analysis), while fine non-granulomatous KPs were found in 71% of the patients with CMV-AU ($p < 0.01$, residual analysis). Pigmented KPs developed during the course of disease in 57% of the patients with HSV-AU, 81% of the patients with ZSH-AU, and 82% of the patients with CMV-AU, with no significant difference. Ring-shaped KPs (Fig. 2) were observed in patients with CMV-AU ($p = 0.00001$, Chi-square test) and were detected in 53% of the patients with CMV-AU ($p < 0.01$, residual analysis).

There was a significant difference in the distribution of KPs (focal or diffuse) among the three groups ($p = 0.006$, Chi-square test). Diffuse large KPs were

Table 2 Clinical features of corneal involvement

	HSV-AU (n = 14)	ZSH-AU (n = 21)	CMV-AU (n = 17)	p value[a]
Keratic precipitates (KPs)	14 (100)	21 (100)	17 (100)	
Morphology of KPs				< 0.01
Mutton-fat	13 (93)**	18 (86)**	5 (29)	
Fine non-granulomatous	1 (7)	3 (14)	12 (71)**	
Pigmented KPs	8 (57)	17 (81)	14 (82)	0.20
Ring-shaped KPs	0 (0)	0 (0)	9 (53)**	< 0.01
Distribution of KPs				< 0.01
Focal	2 (14)	8 (38)	12 (71)**	
Diffuse	12 (86)**	13 (62)	5 (29)	
Corneal edema	7 (50)	7 (21)	8 (47)	0.55
Descemet's membrane folds	2 (14)	8 (38)	3 (18)	0.20
Corneal endotheliitis	3 (21)	0 (0)	6 (35)*	< 0.05
CECs loss[b]	0 (0)	2 (15)	13 (76)**	< 0.01

Data are expressed as number of patients with percent in parenthesis

HSV-AU herpes simplex virus anterior uveitis, *ZSH-AU* varicella zoster virus sine herpete, *CMV-AU* cytomegalovirus anterior uveitis, *CEC* corneal endothelial cells

*$p < 0.05$, residual analysis; **$p < 0.01$, residual analysis

[a]χ^2 test

[b]Specular microscopy was conducted in 7 patients with HSV-AU, 13 with ZSH-AU, and 17 with CMV-AU

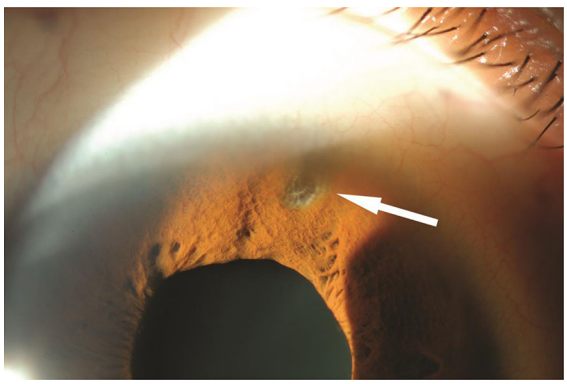

Fig. 2 Keratic precipitates in patients with cytomegalovirus anterior uveitis. **a** Representative slit-lamp photograph showing ring-shaped keratic precipitates on the endothelial surface (arrows). **b** Representative retro-illumination corneal photograph clearly demonstrating the ring-shaped keratic precipitates (arrows)

found in 86% of the patients with HSV-AU ($p < 0.01$, residual analysis) and in 62% of the patients with ZSH-AU ($p > 0.05$), whereas small focal KPs were found in 71% of the patients with CMV-AU ($p < 0.01$, residual analysis). The prevalence of clinically defined corneal endotheliitis was significantly different among the three groups ($p = 0.015$, Chi-square test) and was observed in six patients with CMV-AU (35%; $p < 0.05$, residual analysis). CEC loss was most frequently observed in the CMV-AU group (76%; $p < 0.01$, residual analysis), with a significant difference among the three groups (0/7, HSV-AU; 2/13, ZSH-AU; and 13/17, CMV-AU cases tested; $p = 0.0002$, Chi-square test).

Clinical features of conjunctiva, AC, and iris

The prevalence of ciliary injection and the cell number in the AC were significantly different among the three groups ($p = 0.00002$ and $p = 0.041$, respectively, Chi-square test; Table 3). Ciliary injection was observed in almost all patients with HSV-AU (93%) and ZSH-AU (95%) but only a few patients with CMV-AU (35%) ($p < 0.01$, residual analysis). All patients with HSV-AU and ZSH-AU had grade 1 + or higher cell numbers in the AC, while most patients with CMV-AU had 1 + or lower cell numbers in the AC ($p < 0.05$ and $p < 0.01$, respectively, residual

Table 3 Clinical features of conjunctiva, anterior chamber, and iris

	HSV-AU (n = 14)	ZSH-AU (n = 21)	CMV-AU (n = 17)	p value[a]
Ciliary injection	13 (93)	20 (95)**	6 (35)**	< 0.01
Cells in AC				< 0.05
None	0 (0)	0 (0)	2 (12)**	
Grade 1+	8 (57)	10 (48)	14 (82)*	
Grade 2+	6 (43)	10 (48)	1 (6)	
Grade 3+	0 (0)	1 (4)	0 (0)	
Iris atrophy	7 (50)	16 (76)**	3 (18)**	< 0.01
Round	7**	3	0	
Sectoral	0	13**	0	
Diffuse	0	2	3**	
Pupil distortion	6 (43)	17 (81)**	0 (0)**	< 0.01

Data are expressed as number of patients with percent in parenthesis, or number of patients only

HSV-AU herpes simplex virus anterior uveitis, *ZSH-AU* varicella zoster virus sine herpete, *CMV-AU* cytomegalovirus anterior uveitis, *AC* anterior chamber

*$p < 0.05$, residual analysis; **$p < 0.01$, residual analysis

[a]χ^2 test

analysis). No cells were observed in the AC of two patients with CMV-AU, although these patients had a history of AC inflammation (1 +) before referral to our hospital.

Viral copy number in the AC was the highest in patients with ZSH-AU ($1.2 \pm 1.3 \times 10^7$), followed by HSV-AU ($2.8 \pm 4.4 \times 10^5$) and CMV-AU ($3.1 \pm 6.8 \times 10^4$). The ratio of viral copy number in the three groups (HSV-AU:ZSH-AU:CMV-AU) was approximately 400:10:1. As several reports suggested that CMV was a causative agent for P–S syndrome (12, 13), we investigated the viral DNA of aqueous humor. In five patients with P–S syndrome (56.8 ± 15.9 years old), herpes virus was not detected in the aqueous humor samples.

The prevalence and morphology of iris atrophy were different among the three groups ($p = 0.0016$ and 2.7×10^{-6}, respectively, Chi-square test). The prevalence of iris atrophy was higher in patients with ZSH-AU (76%; $p < 0.01$, residual analysis) and less frequent in those with CMV-AU (18%; $p < 0.01$, residual analysis). Round-shaped iris atrophy (Fig. 3) was observed in all patients with HSV-AU ($p < 0.01$, residual analysis), while patchy or sectoral iris atrophy (Fig. 4) was a typical feature in patients with ZSH-AU (13/21 cases; $p < 0.01$, residual analysis). Diffuse iris atrophy was found in three patients with CMV-AU

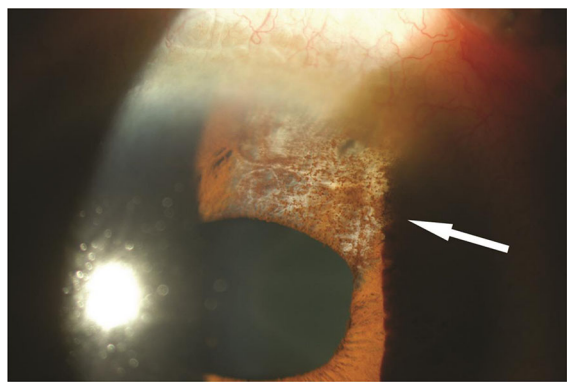

Fig. 3 Iris atrophy in patients with herpes simplex virus anterior uveitis. A representative slit-lamp photograph showing round-shaped iris atrophy (arrow)

($p < 0.01$, residual analysis). In these patients, iris transillumination and posterior synechiae were not observed. Similar to iris atrophy, the prevalence of pupil distortion was different among the three groups ($p = 3.8 \times 10^{-6}$, Chi-square test). Pupil distortion was seen in many patients with ZSH-AU (81%; $p < 0.01$, residual analysis), some patients with HSV-AU (43%), and no patient with CMV-AU ($p < 0.01$, residual analysis). In the patients with iris atrophy or pupil distortion (HSV-AU, ZSH-AU, and CMV-AU: 9, 18, and 3 patients, respectively), only one patient

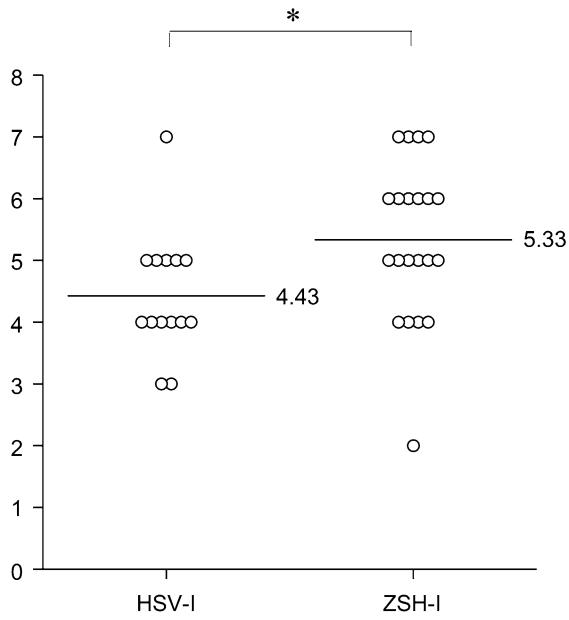

Fig. 4 Iris atrophy in patients with varicella zoster virus anterior uveitis. A representative slit-lamp photograph showing sectoral iris atrophy with distorted pupil (arrow)

with HSV-AU received intraocular surgery (cataract surgery).

Clinical findings and severity of HSV-AU and ZSH-AU

Herpetic iridocyclitis is classified into two groups. There were many common features with the clinical findings of HSV-AU and VZV-AU. Therefore, we compared these groups in order to better clarify their characteristics. Between HSV-AU and ZSH-AU, the viral copy number in the AC was significantly higher in the ZSH-AU group than in the HSV-AU group ($1.2 \pm 1.3 \times 10^7$ vs. $2.8 \pm 4.4 \times 10^5$; $p < 0.01$, Mann–Whitney U test). The severity of iritis between patients with HSV-AU and those with ZSH-AU was then compared. The number of inflammatory findings, such as ciliary injection, Descemet's membrane folds, corneal endotheliitis, mutton-fat KPs, iris atrophy, pupil distortion, and grading of AC cells (1 + to 3 +), was calculated, and an inflammation score was evaluated (each finding was assigned 1 point; range 0–9; Fig. 1). As a result, the inflammation score was statistically higher in the ZSH-AU group (5.33 ± 1.28) than in the HSV-AU group (4.33 ± 1.02; $p = 0.022$, Mann–Whitney U test).

The prevalence of iris atrophy was higher in the ZSH-AU group (16/21 cases) than in the HSV-AU group (7/14 cases), with no statistical difference ($p = 0.110$, Fisher's exact test). However, the morphology was different between the two groups; round-shaped iris atrophy was higher in the HSV-AU group ($p = 0.029$, Fisher's exact test), and sectoral iris atrophy ($p = 0.0001$, Fisher's exact test) and pupil distortion were higher in the ZSH-AU group ($p = 0.025$, Fisher's exact test).

Iris ICGA was also performed to visualize the iris vasculature in five patients with ZSH-AU. While blood flow from the circulus arteriosus major to the circulus arteriosus minor of the iris via a radial vessel was observed, lack of vascular filling was detected corresponding with sectoral iris atrophy (Fig. 5).

Discussion

Herpetic uveitis is a major cause of AU, whereby HSV, VZV, and CMV are recognized as the causative agents. The present study focused on the clinical features of AU and clarified some similarities and differences among AU caused by HSV, VZV, and CMV. Greater awareness of the characteristic clinical features of each viral uveitis is crucial for early diagnosis and appropriate treatment, resulting in better prognosis.

In the present study, the frequent clinical findings of HSV-AU, ZSH-AU, and CMV-AU were subdivided into two groups on the basis of similar presentation. HSV-AU and ZSH-AU were shown to have similar clinical features, such as moderate-to-severe inflammation (ciliary injection and grade 2+ or higher cell numbers in the AC), mutton-fat KP with diffuse distribution, iris atrophy, and pupil distortion. Conversely, CMV-AU tends to occur with recurrent mild iritis with focally distributed fine non-granulomatous KPs or ring-shaped KPs as the common clinical features. Moreover, patients with CMV-AU developed corneal endotheliitis accompanied with a reduced number of CECs.

Together with older age and patients being male, recurrent non-granulomatous mild iritis accompanied with a reduced number of CECs by corneal endotheliitis is considered typical clinical features of CMV-AU. The above clinical findings are considered critical features of herpetic AU because they are similar to

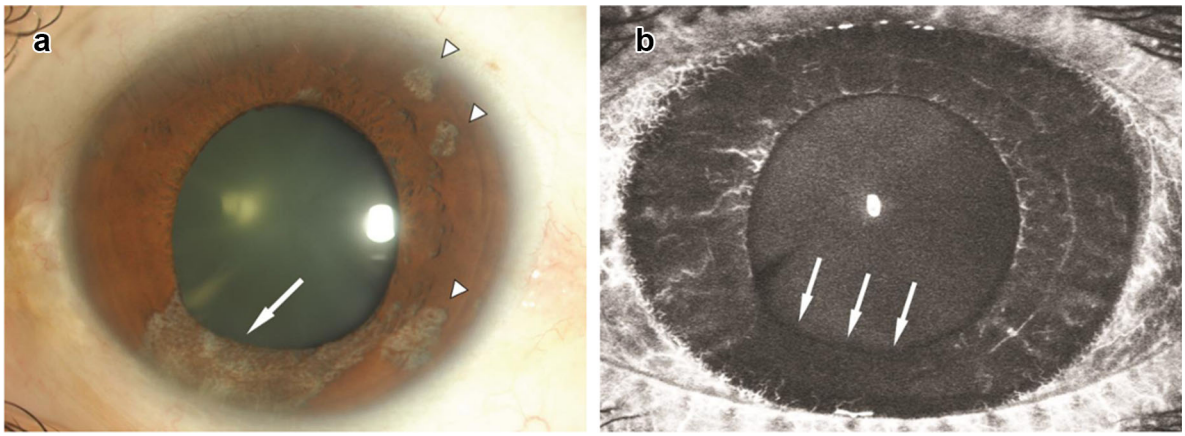

Fig. 5 Iris indocyanine green angiography in patients with ZSH-AU. **a** Sectoral (arrow) and round-shaped iris atrophy (arrowheads) were detected in patients with ZSH-AU. **b** Sectoral iris atrophy was clearly depicted as a loss of the vascular filling area (arrows)

those previously reported in a Japanese study conducted during the same period [26]. In this study, we examined the differences in the degree of ocular inflammation, the number of viral copies, the form of iris atrophy, and reductions in the number of CECs across three different types of herpes virus iritis through the latent and propagation forms of each virus.

In patients with AU, ZSH had the highest viral copy number in the AC, followed by HSV and CMV; the same sequence order was also observed for the severity of AU. Intraocular inflammation was more severe in the ZSH-AU group than in the HSV-AU and CMV-AU groups, whereby patients with CMV-AU revealed quite mild inflammation compared to those with HSV-AU and ZSH-AU. In two patients with CMV-AU, no inflammatory cells were found in the AC during the observation periods, even though these patients had a history of iritis. After latent infection in sensory ganglia, HSV and VZV can reactivate and be transported to the axon terminal (anterograde transport), thereby enabling dissemination of the viruses into epithelial tissue, while latent infection of CMV is established in monocytes [27]. Along with chronic inflammation, monocytes migrate into the AC where dormant CMV in monocytes becomes activated and causes infection in CECs and the trabecular meshwork. Therefore, the pathogenesis of CMV-AU and that of HSV-AU and ZSH-AU are believed to be different. Regarding HSV and VZV, reactivated VZV reportedly migrates to not only sensory ganglion but also satellite cells around sensory ganglion neurons, such as Schwann cells, thereby resulting in the infection of neurons including a large portion of the dermatome, presenting as the herpes zoster rash [28]. In contrast, HSV reactivation is restricted to individual neurons within the ganglion. These differences in viral transmission of HSV, VZV, and CMV may affect the different viral copy numbers in the AC and the resulting severity of AU.

Regarding the pathology of iris atrophy, the prevalence and morphology was also related to the different routes of viral transmission and viral copy number. Patients with ZSH-AU frequently presented with iris atrophy, and the typical morphology was patchy or sectoral iris atrophy. Sectoral iris atrophy specific to ZSH-AU occurs due to ischemic change in the iris, and its pathogenesis is different from the pathogenesis which causes scalloped and well-defined iris atrophy observed in HSV-AU [29]. Types of iris atrophy are different in the infection caused by the three herpes viruses, and the differences are thought to be caused by the difference in the mode of transmission of these viruses. That is, in VZV, where a large amount of reactivated viruses go downward in axon as entangling Schwann cells around nerve fibers, viruses are transmitted to the long posterior ciliary artery which runs adjacent to the axon and occlusive vasculitis in the iris occurs along with sectoral iris atrophy. Different from scalloped and well-defined iris atrophy, it was confirmed by the iris IGGA that sectoral iris atrophy occurs due to occlusion of vascular in the iris; thus, sectoral iris atrophy becomes characteristic findings. Moreover, diffuse iris atrophy occasionally observed in CMV-AU is not accompanied with dyscoria and is

predicted to be caused by persistent ocular hypertension rather than being caused by tissue damage by viruses. In this study, nonperfusion area (NPA) corresponded with the sectoral iris atrophy area but not with the round area on ICGA. In contrast, a correlation between VZV viral copy number and damage to the iris (iris atrophy and pupil distortion) has been reported in patients with herpes zoster ophthalmicus and ZSH [30]. However, our study indicated that there was no correlation between morphology of iris atrophy and viral copy numbers despite the findings of Kido et al. [30]. While HSV and VZV are transmitted from the trigeminal ganglion to the eye via the trigeminal nerve, VZV virus invasion may also occur from the long ciliary nerve to the long posterior ciliary arteries for spreading to the circulus arteriosus major of the iris. Based on the finding of high VZV viral load that infected the eye, sectoral iris atrophy was deemed a characteristic finding in patients with ZSH-AU.

Even though most patients showed corneal endotheliitis and CEC loss, CMV-AU exhibited milder inflammation than HSV-AU and ZSH-AU. While diffuse iris atrophy was found in three patients with CMV-AU, iris transillumination and posterior synechiae were not observed. Therefore, iris atrophy could be associated with persistently high IOP rather than AC inflammation. These findings suggest that the main focus of inflammation induced by CMV involves CECs, and iritis may develop as a secondary reaction, possibly explaining why AC inflammation found in patients with CMV-AU was weak or sometimes absent.

In the present study, CMV was not detected in the aqueous humor of patients with typical P–S syndrome. P–S syndrome is a disease with typically good prognosis and is characterized by mild inflammation in the AC: transient IOP elevation, small-to-medium, non-pigmented KP on the central and inferior cornea, and depigmentation of the trabecular area [22–24]. Although several reports have suggested that CMV is a causative agent of P–S syndrome [12, 13], CMV-AU and typical P–S syndrome should be considered carefully. Although ciliary injection and pigmented KPs were found in 35% (6/17 patients) and 82% (14/17 patients), respectively, in CMV-AU, none of these findings were noted in patients with P–S syndrome [22]. In addition to ring-shaped KPs and a decreased number of CEC, the presence of ciliary injection and pigmented KPs may be useful findings to differentiate between CMV-AU and P–S syndrome. Depigmentation of the trabecular area observed in the affected eye of patients with P–S syndrome is also an important finding to distinguish between the two. However, the pathogenesis of CMV-AU remains unclear. Additional investigations on CMV-AU are needed to clarify the pathogenesis of this disease, including the predominance of male patients.

Conclusion

In summary, while AU caused by various herpes viruses shares common clinical features, each type of AU exhibits distinct characteristic findings. Although a small number of patients were examined, these results may help with the diagnosis of herpetic AU and to clarify the pathomechanisms of each type of AU.

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Compliance with ethical standards

Conflict of interest The author reports no conflicts of interest in this work.

Research involving human participants and/or animals For this type of study, formal consent was not required.

Informed consent Informed consent was obtained from all participants included in the study.

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