

1 Article Type : A Case Report

2 Clinical Features of Keratouveitis Associated with Cytomegalovirus Infection

3 巨細胞病毒導致角膜葡萄膜炎之臨床表現

4 Peng-Tai Tien, M.D.<sup>1</sup>, Yi-Yu Tsai, PhD.<sup>1</sup>, Tsai-Hsiu Lin, M.D.<sup>2</sup>, Chun-Chi Chiang,

5 MD.<sup>1</sup>

6 田彭太<sup>1</sup>，蔡宜佑<sup>1</sup>，林彩秀<sup>2</sup>，江鈞綺<sup>1</sup>

7 1. Department of Ophthalmology, China Medical University Hospital

8 中國醫藥大學附設醫院眼科部

9 2. Department of Laboratory Medicine, China Medical University Hospital

10 中國醫藥大學附設醫院檢驗醫學部

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13 Reprint Requests : Chun-Chi Chiang, Department of Ophthalmology, China Medical

14 University Hospital, No 2, Yuh-Der Road, Taichung 404, Taiwan

15 聯絡地址：404，台中市育德路2號，中國醫藥大學附設醫院眼科部，江鈞綺

16 E-mail address: u702054@hotmail.com

17 TEL : 886-4-22052121 (ext. 1141)

18 FAX : 886-4-22052121 (ext. 1139)

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1 **Abstract**

2 Purpose: To report a case of keratouveitis associated with cytomegalovirus infection

3 Method: Interventional case report

4 Result: We examined a 44-year-old male who had been suffering from recurrent  
5 elevated intraocular pressure (IOP) in the left eye for 2 years. The ocular manifestations  
6 included stromal and epithelial microcystic corneal edema, keratic precipitates, and  
7 elevated IOP. The lesion did not subside after treatment with oral valganciclovir for a  
8 week. The cytomegalovirus (CMV) genome was detected in the aqueous humor by  
9 means of the polymerase chain reaction (PCR). The IOP was controlled by performing a  
10 trabeculectomy. Treatment with intravenous ganciclovir (450 mg, Q12H \* 1 week)  
11 followed by oral valganciclovir (900 mg BID) for 2 months returned the cornea to  
12 complete clarity without keratic precipitates. The IOP also returned to the normal range.  
13 However, we detected a low endothelial cell density of the affected cornea by specular  
14 microscopy.

15 Conclusion: The clinical presentation of CMV keratouveitis may resemble that of  
16 Posner-Schlossman syndrome or Fuchs heterochromic iridocyclitis. If CMV  
17 keratouveitis is suspected, then early PCR analysis of the aqueous humor could lower  
18 the rate of delayed diagnosis. Compared with intravenous ganciclovir, oral

1 valganciclovir not only shortens the hospitalization period but also offers greater  
2 convenience to patients.

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1 摘要

2 目的：報告與巨細胞病毒感染有關之角膜葡萄膜炎一例

3 方法：病例報告

4 結果：一位 44 歲男性左眼眼壓上升反覆發作已兩年，眼部表現包含角膜基質/上

5 皮小泡性水腫、角膜沉降物及眼壓上升。病灶在口服 valaciclovir 一個月後並無消

6 退，經房水聚合酶鏈鎖反應偵測到巨細胞病毒基因組。施行小樑切除術以控制眼

7 壓，在接受靜脈注射 ganciclovir (450 mg，每 12 小時一次共 1 周) 並接續口服

8 valganciclovir (900 mg，一天兩次) 兩個月後，角膜完全透明且原有角膜沉降物消

9 失，眼壓亦回到正常範圍；然而角膜細胞數目測定儀卻偵測到受影響角膜之低內

10 皮細胞密度。

11 結論：巨細胞病毒角膜葡萄膜炎之臨床表現可能與 Posner-Schlossman syndrome

12 及 Fuchs heterochromic iridocyclitis 類似，當高度懷疑角膜葡萄膜炎時，即早施行

13 單純疱疹病毒及巨細胞病毒房水聚合酶鏈鎖反應檢驗將有助於降低延遲診斷之機

14 率。相較於靜脈注射 ganciclovir，口服 valganciclovir 不單單可縮短住院天數，亦

15 帶給患者較大的便利性。

16 **Key words**

17 Cytomegalovirus, Keratouveitis, Polymerase chain reaction, Valganciclovir

18 巨細胞病毒，角膜葡萄膜炎，聚合酶鏈鎖反應，克毒癒

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1 Cytomegalovirus (CMV) infection is very common in humans, and most of the  
2 infected patients have no symptoms. Although ocular manifestations (retinitis) are found  
3 in immunocompromised patients, involvement of the anterior segment is comparatively  
4 mild and less common.<sup>1</sup> However, it has been found that ocular CMV infection is  
5 associated with corneal endotheliitis and hypertensive anterior uveitis in  
6 immunocompetent humans.<sup>2,3</sup>

7 We report a rare case of CMV keratouveitis with sector corneal edema, keratic  
8 precipitates, iris depigmentation, and elevated intraocular pressure (IOP), which  
9 mimicked Posner-Schlossman syndrome (PSS) and Fuchs heterochromic iridocyclitis  
10 (FHI) in a relatively healthy man.

## 1   **CASE REPORT**

2       A 44-year-old Chinese man was referred to our out-patient department (OPD)  
3       because he had been suffering from gradually blurring vision in the left eye for the past  
4       2 years. An examination revealed that recurrent episodes of elevated IOP occurred  
5       during this period. The interval between each occurrence of elevated IOP was  
6       approximately 1 month, and each episode initially subsided following topical  
7       medication (including steroids). As the symptoms progressed, the intervals shortened  
8       and the patient's response to medical treatment became poorer.

9       At presentation, we noted corneal edema (superior-nasal quadrant). The best-  
10       corrected visual acuity of the right and left eyes was 20/20 and 20/200, respectively. The  
11       IOP was 16 mmHg in the right eye and 74 mmHg in the left. After emergent anti-  
12       glaucomatic medical management, the IOP in the left eye decreased to 23 mmHg. The  
13       initial diagnosis was Posner-Schlossman syndrome (PSS).

14       The patient returned to our OPD the next day; an examination of the cornea at the  
15       time revealed microcystic and stromal edema extending to the upper half (Figure 1-A)  
16       with keratic precipitates (KPs; Figure 1-B/C). We also observed cells (++) in the  
17       anterior chamber. The iris was depigmented compared to the fellow eye, mimicking the  
18       presentation of Fuchs heterochromic iridocyclitis (FHI; Figure 1-D). The lens

1 demonstrated moderate posterior subcapsular opacity. There was no vitritis or retinitis.

2 The IOP was 18 mmHg in the left eye.

3 We suspected herpes simplex virus (HSV) infection or varicella zoster virus (VZV)  
4 infection related to hypertensive anterior uveitis because of the presence of sector  
5 corneal edema and KP's; therefore, we initially prescribed valaciclovir (1 gm twice a  
6 day). However, after 1 week of oral valaciclovir treatment, the lesion progressed and  
7 extended toward the lower part of the cornea with coin-shaped KPs (Figure 2). Hence,  
8 CMV infection was highly suspected, and the aqueous humor tap was performed to  
9 investigate this possibility.

10 CMV DNA was extracted with a QIAGEN<sup>®</sup> Blood DNA mini kit (QIAGEN Inc, CA,  
11 USA). Purified viral DNA was resuspended in 60 µl buffer AE. The PCR mixture  
12 contained virus DNA, 10x PCR reaction buffer, 3.6 mM MgCl<sub>2</sub>, 0.2 mM (each)  
13 deoxynucleoside triphosphates, 20 pmol of each primer. Then 1 U of Taq DNA  
14 polymerase was added after denaturing the DNA at 94°C for 5 min. DNA amplification  
15 was performed with 40 cycles, each cycle consisting of denaturation for 2 min at 94°C,  
16 primer annealing for 2 min at 63°C, extension for 3 min at 72°C, and a final extension  
17 step at 72°C for 10 min. The PCR products were analyzed by electrophoresis in 2%  
18 agarose gels stained with ethidium bromide. The PCR analysis revealed the presence of

1 the cytomegalovirus genome. (Figure 3)

2 After the diagnosis of CMV keratouveitis in the left eye, the patient was admitted for  
3 intravenous ganciclovir therapy (450 mg Q12H). The corneal edema and KP's did not  
4 resolve after 2 days of hospitalization (Figure 4). The IOP in the left eye remained  
5 recalcitrant (37~39 mmHg) despite maximal topical therapy with Cosopt<sup>®</sup> (dorzolamide  
6 and timolol), Alphagan<sup>®</sup> (brimonidine), and oral Diamox<sup>®</sup> (acetazolamide). Therefore, a  
7 trabeculectomy was performed on the third day of hospitalization. The bleb persisted  
8 and the IOP in the left eye returned to the normal range on the following day.  
9 Concurrent blood serology provided negative results for CMV immunoglobulin M,  
10 human immunodeficiency virus (HIV) antibodies, and CMV antigen (pp65), but  
11 positive results for CMV immunoglobulin G antibody. After 7 days of intravenous  
12 ganciclovir therapy, the patient was discharged with oral valganciclovir (900 mg BID)  
13 and topical Pred Forte<sup>®</sup> (prednisolone acetate, QID).

14 After oral valganciclovir therapy for a month, corneal edema was found to be  
15 confined only to the superior-nasal corner as a crescent lesion (Figure 5-A). The IOP  
16 was 17 mmHg in the right eye and 12 mmHg in the left eye. Although iris  
17 depigmentation persisted, KPs were no longer observed (Figure 5-B). Specular  
18 microscopy showed low endothelial cell density (408/mm<sup>2</sup>) in the left eye (Figure 5-C).



1 The cornea was completely clear after oral valganciclovir therapy for 7 weeks. The IOP  
2 in the left eye was 18 mmHg.

3 We ceased all medication after the second month of therapy. Serologic examination  
4 revealed normal renal and liver functions. There was no regression of the corneal lesion  
5 after valganciclovir treatment had been stopped for 2 months (Figure 6-A). The patient  
6 underwent a repeated aqueous humor tap, and PCR analysis revealed negative CMV  
7 results (Figure 6-B).

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## 1 **DISCUSSION**

2 Although the pathogenesis of CMV keratouveitis remains poorly understood,  
3 Koizumi et al. presumed that anterior chamber-associated immune deviation (ACAID)  
4 prevents the control of viral proliferation by cell-mediated immunity while CMV is  
5 reactivated in the anterior chamber. Thus, CMV infection may develop in the corneal  
6 endothelium.<sup>4</sup>

7 Different ocular manifestations in CMV keratouveitis cases have been observed in  
8 other institutions (Table 1). In April 2009, a patient at the National Cheng Kung  
9 University Hospital presented with corneal edema and elevated IOP, which was  
10 refractory to valaciclovir treatment. A case series from the Singapore National Eye  
11 Centre provided the following observations: (1) corneal edema may be focal to diffuse  
12 bullous keratopathy, with some cases showing a distinct horizontal curvilinear  
13 demarcation on the endothelium; (2) KPs varied in appearance from a linear pattern to a  
14 circular (coin-shaped) pattern; (3) mild anterior chamber inflammation; (4) iris atrophy;  
15 (5) lens opacity in some cases; and (6) elevated IOP.<sup>3, 5, 6</sup> Koizumi et al. also reported  
16 that (1) stromal edema of the cornea was found in all CMV infected eyes; (2) linear KPs  
17 and coin-shaped lesions were commonly observed in CMV-induced corneal  
18 endotheliitis. They also described variously as KPs having a circular pattern or ring

1 configuration; (3) anterior chamber inflammation; (4) elevated IOP.<sup>4</sup>

2 The 2 common features of the reported CMV keratouveitis cases were elevated IOP  
3 and iris atrophy, and they are consistent with the findings of CMV infection in the  
4 smooth muscle cells of the iris, ciliary body, and the endothelial cells of Schlemm's  
5 canal.<sup>1</sup> However, CMV keratouveitis could easily be misdiagnosed as other conditions  
6 with hypertensive anterior uveitis such as PSS and FHI. PSS is characterized by  
7 recurrent episodes of mild inflammation with elevated IOP, fine KP's, and corneal  
8 epithelial edema, with the IOP returning to normal between successive episodes. FHI is  
9 characterized by iris heterochromia, posterior subcapsular opacity cataract, and satellite  
10 KP's. Chee et al. demonstrated that CMV infection can cause a spectrum of ocular  
11 manifestations resembling PSS, FHI, or even corneal endotheliitis.<sup>5</sup> A comparison of  
12 the CMV-positive PSS and FHI patients in Chee et al.'s case series revealed that the  
13 PSS patients were younger, had higher IOP, and were less likely to have iris atrophy or  
14 cataracts. Nodular endothelial lesions were more commonly observed in CMV-positive  
15 FHI eyes than in CMV-positive PSS eyes, and they probably represent CMV-infected  
16 endothelial cells. Reticulate cornea deposits were highly predictive of CMV retinitis as  
17 they were observed in all of the potential FHI eyes but not in the potential PSS eyes.  
18 Chee and Jap hypothesized that these manifestations are dependent on the ocular

1 immune response and/or viral load. Eyes resembling PSS are probably the result of the  
2 inflammatory response to CMV infection as they respond to topical steroids alone and  
3 may even be self-limiting. On the other hand, eyes resembling FHI may have a larger  
4 viral load and/or poorer immune response than eyes resembling PSS, given their poor  
5 response to steroids.<sup>6</sup>

6 We used 2 pairs of primers for our CMV PCR analysis. One pair amplifies a 400-base-  
7 pair sequence that codes for a portion of the late antigen (LA) of CMV (AD169 strain)  
8 which is composed of LA-1 (5'-CAC CTG TCA CCG CTG CTA TAT TTGC-3') and  
9 LA-6 (5'-CAC CAC GCA GCG GCC CTT GAT GTTT-3'). The other pair amplifies a  
10 435-base-pair sequence that codes for a portion of the major immediate-early (MIE)  
11 antigen of CMV (Twone strain), which is composed of MIE-4 (5'-CCA AGC GGC CTC  
12 TGA TAA CCA AGC C-3') and MIE-5 (5'-CAG CAC CAT CCT CCT CTT CCT CTG  
13 G-3'). The analysis provided a sensitivity of 93% with a specificity of 100%.<sup>7</sup> Although  
14 these primers for CMV PCR analysis are also used in other institutions<sup>4,8,9</sup> (Table 2),  
15 other primer sets are also used: 5'-TTA GTG AAC CGT CAG ATC GC and 3'-GCA  
16 TGC ATA AGA AGC CAA GG are used in the Ehime University School of Medicine<sup>4</sup>,  
17 while 5'-CAC TTC GGG GTC GCA AT and 5'-CGG GTA TCA ACA ACA GCA  
18 AGGA are used in the Tan Tock Seng Hospital<sup>10</sup>.

1 Blood serology provided positive results for the CMV immunoglobulin G antibody  
2 and negative for the CMV antigen and immunoglobulin M antibody. These facts  
3 revealed that the patient had a prior systemic CMV infection, but the current CMV  
4 infection was limited to the eye alone and it was not a spillover from a systemic  
5 infection. CMV infection can also be determined by quantifying the levels of intraocular  
6 and serum immunoglobulin G antibodies. The ratio of the quantities of intraocular  
7 immunoglobulin G antibody to serum immunoglobulin G antibody is called the  
8 Goldmann–Witmer coefficient (C).  $C > 1$  indicates the intraocular production of  
9 antibodies, while  $C > 3$  is considered significant. This analysis has a sensitivity of  
10 47.3% and a specificity of 98.0%.<sup>11</sup>

11 In order to diagnose CMV keratouveitis, it is necessary to perform PCR analysis or  
12 the intraocular antibody assay (Goldmann-Witmer coefficient). In our laboratory, at  
13 least 100  $\mu$ l of aqueous sample was needed for each pathogenic PCR. At least 200  $\mu$ l of  
14 aqueous sample was needed for the intraocular antibody assay. As the amount of tapped  
15 aqueous humor was limited and the intraocular antibody assay is not more sensitive than  
16 PCR<sup>2</sup>, we preferred to conduct only the PCR analysis.

17 Although several infective pathogens (such as HSV, VZV, or *Toxoplasma* spp.) may  
18 result in hypertensive uveitis, which has symptoms similar to those of CMV

1 keratouveitis, only PCR analyses for CMV and HSV are available in our laboratory. As  
2 the patient received refractory valaciclovir therapy for 1 week, we only performed PCR  
3 analysis for CMV. However, PCR analyses for both CMV and HSV were performed for  
4 suspected keratouveitis cases currently and at least 200 µl of aqueous sample was  
5 needed. In recent years, tetraplex PCR analysis was developed by the Singapore General  
6 Hospital. It simultaneously detects HSV, VZV, CMV, and *T. gondii*. Only 100 µl of  
7 aqueous sample is needed for this analysis, which has a sensitivity and specificity of  
8 more than 95%.<sup>3,5</sup>

9 CMV corneal endotheliitis can initially present as hypertensive anterior uveitis and  
10 thereafter lead to sustained corneal damage that only responds to treatment with  
11 steroids.<sup>3</sup> Repeated use of steroids may lead to favorable conditions for viral replication,  
12 which leads to increasingly frequent attacks and glaucomatous damage.<sup>6</sup> PCR analysis  
13 of aqueous humor plays an important role in detecting specific viral infections. We  
14 suggest that aqueous humor PCR analysis for HSV/CMV be performed immediately  
15 when viral keratouveitis is highly suspected, So that the rate of delayed diagnosis can be  
16 decreased.

17 The traditional treatment of CMV infection is intravenous ganciclovir (5 mg/kg  
18 Q12H) for 3 weeks and requires the patient to be admitted to a hospital. However, this

1 treatment is very inconvenient for the patient. We prescribed oral valganciclovir after  
2 the patient was discharged. Valganciclovir is the prodrug of ganciclovir and is available  
3 in oral form. The advantage of valganciclovir is not only the reduced period of  
4 hospitalization but also a good therapeutic effect.

5 Our patient received intravenous ganciclovir (450 mg twice daily for a week),  
6 followed by oral valganciclovir (900 mg twice daily for another 8 weeks). Until now,  
7 the patient has had regular follow-ups for 9 months since the cessation of valganciclovir  
8 therapy and there have been no recurrent episodes in the absence of antiviral or anti-  
9 glaucomatic therapy during this period. The subjects from the case series of Chee et al.  
10 received oral valganciclovir (900 mg twice daily for 6 weeks, followed by 450 mg twice  
11 daily for another 6 weeks) or intravenous ganciclovir (5 mg/kg body weight twice daily  
12 for 6 weeks), followed by oral ganciclovir (1 g three times daily for another 6 weeks).  
13 However, 77.7% of the subjects had a recurrence within 8 months of stopping the  
14 treatment and required further courses of ganciclovir, although it was not specifically  
15 mentioned if these subjects belonged to the ganciclovir group or the valganciclovir  
16 group, or both. Hence, CMV keratouveitis may require a longer period of treatment.<sup>5</sup>

17 In conclusion, we identified a case with CMV keratouveitis whose ocular  
18 manifestations resembled PSS, FHI, and corneal endotheliitis. It is important to perform

- 1 aqueous humor PCR analysis in order to ensure correct diagnosis of CMV keratouveitis.
- 2 In addition to intravenous ganciclovir treatment, oral valganciclovir is a new option for
- 3 treating CMV keratouveitis.<sup>3,5</sup>
- 4



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## 1 **FIGURE LEGENDS**

2 FIGURE 1. Patient with keratouveitis. Slit-lamp photograph showing (A) microcystic  
3 and stromal edema extending to the upper half of the left cornea. The iris was  
4 depigmented. (B/C) Fine keratic precipitates. (D) The right iris was fully pigmented.

5 FIGURE 2. One month after oral acyclovir treatment. (A) The original edema extended  
6 towards the lower part of the cornea. (B) A slit lamp revealed coin-shaped keratitic  
7 precipitates, stromal edema, and iris depigmentation.

8 FIGURE 3. Electrophoresis of aqueous humor PCR products. CMV pp65 and CMV  
9 pp71 were confirmed in the sample (Lane 4/7)

10 FIGURE 4. Two days after intravenous ganciclovir treatment. (A) The original edema  
11 did not subside. (B) Iris depigmentation. (C, D) Coin-shaped keratitic precipitates,  
12 stromal edema, and epithelial microcystic edema.

13 FIGURE 5. One month after oral valganciclovir treatment. (A) The original edema was  
14 confined to the superior-nasal corner as a crescent lesion. (B) There was an absence of  
15 keratic precipitates. (C) Low endothelial cell density ( $408/\text{mm}^2$ ) in the left eye.

16 FIGURE 6. After ceasing valganciclovir treatment for 2 months. (A) There was no  
17 regression of the corneal lesion. (B) Aqueous humor PCR revealed no presence of CMV  
18 pp65 or CMV pp71.

1 Table 1. Ocular manifestations of CMV keratouveitis

Cases	Numbers	Corneal Edema	KPs	A/C Inflammation
<b>Tien et al.<sup>*</sup></b>	1	+	+	+
<b>Chen et al.<sup>+</sup></b>	1	+	+	+
<b>Chee et al. (2002~2005)<sup>3</sup></b>	12	12/12	12/12	12/12
<b>Chee et al. (2004~2006)<sup>5</sup></b>	24	24/24	24/24	24/24
<b>Koizumi et al.<sup>4</sup></b>	8	8/8	8/8	8/8

2

3 Continued

Cases	Elevated IOP	Lens Opacity	Iris Atrophy
<b>Tien et al.<sup>*</sup></b>	+	+	+
<b>Chen et al.<sup>‡</sup></b>	+	Not mentioned	+
<b>Chee et al. (2002~2005)<sup>3</sup></b>	12/12	9/12	8/12
<b>Chee et al. (2004~2006)<sup>5</sup></b>	24/24	Not mentioned	13/24
<b>Koizumi et al.<sup>4</sup></b>	6/8	Not mentioned	Not mentioned

4 <sup>\*</sup>, China Medical University Hospital; <sup>‡</sup>, National Cheng Kung University Hospital

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1 Table 2. LA-1/LA-6 and MIE-4/MIE-5 are commonly used to detect CMV with PCR  
2 analysis

<b>Institution</b>	<b>Primers</b>
China Medical University Hospital	LA-1/LA-6; MIE-4/MIE-5
Osaka University Medical School	LA-1/LA-6; MIE-4/MIE-5
Kyoto Prefectural University of Medicine	LA-1/LA-6
General Hospital of Athens	MIE-4/MIE-5

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