Case report

CYTOMEGALOVIRUS-ASSOCIATED ANTERIOR UVEITIS PRESENTING AS FUCHS’ HETEROCHROMIC UVEITIS SYNDROME: A CASE REPORT

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Abstract

Purpose To investigate the etiologic organism in an immunocompetent patient with uveitis typical of Fuchs’ heterochromic uveitis syndrome (FHUS) by aqueous humor and vitreous humor analysis.

Design Case report and review of literature

Method The aqueous and vitreous fluid samples from a female patient with FUCHs’ heterochromic uveitis syndrome, who consulted the Uveitis Clinic of the Department of Ophthalmology, Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University, were analyzed for Rubella virus, Cytomegalovirus (CMV), Herpes Simplex Virus-1 (HSV-1), Herpes Simplex Virus-2 (HSV-2), Varicella Zoster Virus (VZV) and Toxoplasma gondii (T. gondii) DNAs by real-time polymerase chain reaction (PCR). Comparison of specific antibody production in ocular fluid and plasma was determined by Goldmann-Witmer coefficient (GWC) analysis. The clinical data, ocular findings and treatment were also reviewed.

Results Positive CMV DNA and GWC analyses were found in the vitreous fluid. Meanwhile, aqueous fluid examination showed all negative results.

Conclusion CMV infection was identified in a vitreous sample of an immunocompetent patient with uveitis typical for FHUS. Chiang Mai Medical Journal 2009;48(2):71-76.

Keywords: FUCHs’ heterochromic uveitis syndrome, cytomegalovirus, polymerase chain reaction, Goldmann-Witmer coefficient
Fuchs’ heterochromic uveitis syndrome (FHUS), or Fuchs’ heterochromic iridocyclitis, is a chronic low-grade intraocular inflammation, which is typically associated with iris heterochromia, absence of synechiae and cataract.\(^1\)\(^2\) Frequently, vitreous opacities are also present. Traumatic, genetic, infectious and immune-mediated factors were thought to be possible implications in the pathogenesis of FHUS; specifically, infections with *Toxoplasma gondii* (*T. gondii*), *Toxocara canis* (*T. canis*), rubella and herpes viruses that were all considered involved in the development of this clinical syndrome.\(^1\)\(^3\) Currently, an increased antibody index and positive polymerase chain reaction (PCR) for rubella virus in intraocular fluids of patients with FHUS are documented in Europe.\(^4\)\(^5\) In contrast, studies from Singapore have shown that FHUS might also be associated with intraocular cytomegalovirus (CMV) infection.\(^6\) Herein, we report on an immunocompetent Thai patient with unilateral FHUS, in whom PCR analysis of intraocular fluids and Goldmann-Witmer coefficient (GWC) were documented with CMV infection.

**Case report**

A 42-year-old immunocompetent, human immunodeficiency virus (HIV) negative Thai female presented with a slow decrease of vision in her left eye. In a left eye examination, visual acuity was 20/80. The whole corneal endothelial surface was covered with diffusely fine stellate keratic precipitates (Figure 1). The anterior chamber contained 2+cells and there were no synechiae present. The iris exhibited no heterochromia or nodules, but there was generalized stromal atrophy leading to loss of crypts. The lens showed posterior subcapsular cataract. There were 2+cells and opacities present in the anterior vitreous. Retinal findings and intraocular pressure were normal. Right eye examination was normal. The clinical diagnosis of FHUS was made and the patient was treated with topical steroids, without effect however. The patient underwent cataract extraction during which the diagnostic intraocular samples and serum were collected.

**Methods**

Sample Collection and Analysis Intraocular fluid (aqueous and vitreous) and plasma samples were collected. All samples were stored at -20 °C before performing laboratory analysis.

Intraocular fluids were examined for the presence of rubella, CMV, herpes simplex virus (HSV-1, HSV-2), varicella zoster virus (VZV) and *T. gondii* DNA by real-time PCR analysis. Nucleic acid was extracted from 25 μL of intraocular fluids using the QIAamp® DNA blood Mini Kit (QIAGEN, USA). To monitor the quality of the extraction and the amplification procedure, 2,500 to 5,000

![Figure 1. Anterior segment photography showing the whole corneal endothelial surface covered with diffusely fine stellate keratic precipitates.](image-url)
copies/ml of Seal herpes virus type 1; Phocid herpes virus type 1 (PhHV-1) was added to each sample before extraction.\(^7\)\(^9\) The detection of CMV, HSV-1, HSV-2, VZV and \emph{T. gondii} DNAs was performed on the Chromo4\textsuperscript{TM} real-time PCR detector (DNA Engine\textsuperscript{®} Pelter Thermocycler, BIO-RAD) at the Division of Clinical Microbiology, Department of Medical Technology, Chiang Mai University. The detection of rubella virus DNA by real-time PCR analysis was performed on the ABI Prim 7700 sequence detection system (Applied Biosystems) at the Department of Virology, University Medical Center Utrecht, The Netherlands. The primers and probes used in this study were published previously.\(^12\)

In addition, Goldmann-Witmer coefficient (GWC) was determined to assess the active intraocular production of specific antibodies in the eye to rubella virus, CMV and VZV, by methods previously described.\(^10\) The amount of specific immunoglobulin G (IgG) against Rubella, CMV and VZV, in serum and intraocular fluid, was determined by the Enzygnost\textsuperscript{®} Anti-Rubella/IgG, Anti-CMV/IgG and Anti-VZV/IgG ELISA kits (Dade Behring), respectively. The assays were performed according to the manufacturer’s instructions. The total IgG was determined by an in-house ELISA using commercially available reagents. To determine the total IgG concentration, seven serial twofold dilutions of a nephelometer N Protein standard SL (Dade Behring) were included. Active intraocular antibody production was considered positive when the GWC value was greater or equal to 3.\(^10\)\(^12\)

**Results**

The patient tested positive in vitreous analysis for CMV in PCR and GWC analyses. However, in aqueous analysis, detections of the DNAs of rubella virus, CMV, HSV-1, HSV-2, VZV and \emph{T. gondii} were all negative. The GWC analysis of aqueous sample also presented negative results for CMV, VZV and rubella virus infection. The detection of CMV DNA in vitreous analysis, and a strongly positive GWC of 40, confirmed the intraocular CMV infection in this FHUS patient.

After the diagnosis of CMV-associated uveitis was made, the patient was treated 6 times with repeated intravitreal ganciclovir injections (2 mg in 0.05 mL). However, the intraocular inflammation did not improve and cystoid macular edema developed. The anterior and vitreous sampling was repeated during therapeutic vitrectomy and tested negative for CMV in both aqueous and vitreous samples. Unfortunately, the patient’s final visual acuity of the left eye was counting finger, due to persistent cystoid macular edema.

**Discussion**

CMV infection was identified in a vitreous sample of an immunocompetent patient with uveitis typical of FHUS. For many years, FHUS represented a mysterious disease, which showed poor response to steroid treatment. Although the exact etiology of FHUS is not yet fully elucidated, infection is considered to be a most important causative factor. An association between rubella virus infection and FHUS was documented in Europe, specifically intraocular production of antibodies against the rubella virus, which was detected in almost 90% of patients with FHUS.\(^4\)\(^5\) It is probable that the rubella virus is not the only cause of FHUS, since an
association between FHUS and herpes viruses, especially CMV, was repeatedly documented in Asian patients.\(^{13-16}\) Although intraocular infection with CMV (especially CMV retinitis) was previously associated with immunosuppression, CMV-associated anterior uveitis is increasingly being recognized in immunocompetent patients.\(^6\) It is possible that the clinical syndrome of FHUS might be caused by different infectious microorganisms. Therefore, the etiology cannot be based on clinical features alone, and for a definitive diagnosis, an analysis of intraocular fluid is required.

In general, aqueous analysis is used for diagnosing of anterior eye disease, while vitreous samples are more suitable for disorders of the posterior eye segment.\(^{17}\) It is not known which ocular structures are affected by CMV in patients with FHUS. Our patient illustrates that aqueous analysis might be negative, while vitreous analysis might be positive for CMV in a patient with FHUS. Our patient had no retinal scars or active retinal lesions; the only visible involvement of posterior segment consisted of vitreous cells and opacities. She indicated that despite the presence of anterior uveitis, CMV could not be detected in the anterior chamber, but was clearly present in the posterior eye segment. This finding could be caused by the lesser amount of fluid from aqueous compare to vitreous samples and less sensitivity of the aqueous analysis in detection of CMV DNA by the PCR technique.\(^{18}\) If only aqueous samples were studied, then the cause of uveitis in our patient would not have been solved.

**Conclusion**

We report an immunocompetent Thai patient with Fuchs’ heterochromic uveitis syndrome that was caused by CMV. PCR and GWC techniques were helpful in identifying of infectious agents in intraocular samples. Future studies identifying the infectious agents that cause intraocular inflammation will be useful for successful management of affected patients.

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**References**

รายงานผู้ป่วย: การติดเชื้อ CYTOMEGALOVIRUS ที่สัมพันธ์กับการเกิดภาวะ FUCHS’ HETEROCROMIC UVEITIS SYNDROME

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บทคัดย่อ
วัตถุประสงค์ เพื่อหาเชื้อสาเหตุที่ทำให้เกิดภาวะ Fuchs’ heterochromic uveitis syndrome (FHUS) ในผู้ป่วยโรคตาส่วนยูเวียอักเสบ (uveitis) ซึ่งมีระบบภูมิคุ้มกันปกติ โดยการตรวจวิเคราะห์น้ำในช่องหูถุงตา (aqueous humor) และน้ำวุ้นลูกตา (vitreous humor)

วิธีการทดลอง
ทำการตรวจวิเคราะห์ตัวอย่างน้ำลูกตาของผู้ป่วยหญิงที่มีภาวะ FHUS จำนวน 1 ราย ซึ่งเข้ารับการรักษาที่คลินิกโรงพยาบาลมหาวิทยาลัยเชียงใหม่ โดยการตรวจหาระงับพันธุกรรมของเชื้อยืดซึ่งคาดว่าจะเป็นสาเหตุของกรณีโรค ซึ่งได้แก่เชื้อ Rubella virus, Cytomegalovirus (CMV), Herpes simplex Virus-1 (HSV-1), Herpes simplex Virus-2 (HSV-2), Varicella Zoster virus (VZV) และ Toxoplasma gondii (T. gondii) ด้วยเทคนิค real-time polymerase chain reaction (PCR) ร่วมกับการวิเคราะห์แอนติบอดีที่จำเพาะต่อเชื้อดังกล่าวในน้ำลูกตาและน้ำวุ้นลูกตา ของผู้ป่วยด้วยการวิเคราะห์ Goldmann-Witmer coefficient (GWC) ตลอดจนทำการประมวลผลการตรวจวิเคราะห์น้ำลูกตาและน้ำวุ้นลูกตา

ผลการทดลอง
หลังจากตรวจหาระงับพันธุกรรมของเชื้อด้วยเทคนิค real-time PCR พบในภาวะ FHUS สามารถตรวจหาระงับซึ่งเชื้อ CMV ได้ในน้ำลูกตา ซึ่งสองหลักสอดคล้องกับการตรวจหาระงับเชื้อ CMV ด้วยวิธี GWC ได้แก่การตรวจหาระงับซึ่งเชื้อ CMV ได้แก่การตรวจหาระงับซึ่งเชื้อ CMV ด้วยวิธี GWC ในการตรวจหาระงับพันธุกรรม real-time PCR และการวิเคราะห์ GWC

สรุป สาเหตุจากการเกิดภาวะ FHUS ในผู้ป่วยโรคตาส่วนยูเวียอักเสบที่มีภาวะภูมิคุ้มกันปกติอาจเกิดจากการติดเชื้อ CMV สามารถตรวจพบได้ในน้ำลูกตา ซึ่งน้ำลูกตา ของผู้ป่วย FHUS 2552;48(2):71-76.

คำสำคัญ: Fuchs’ heterochromic uveitis syndrome, cytomegalovirus, polymerase chain reaction, Goldmann-Witmer coefficient