



Case Report

Recalcitrant infectious uveoscleritis: A case report of a coinfection by Epstein-Barr virus and *Talaromyces marneffe*

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ABSTRACT

Introduction and importance: In an immunocompromised patient, there has never been a report of Epstein-Barr virus (EBV) and *Talaromyces marneffe* co-infection. Treatment with intravenous ganciclovir for EBV-associated uveitis has only been explored in a few cases.

Case presentation: A 47-year-old HIV-positive female presented with scleral nodule and vascularized iris tumor in the left eye. After the ancillary laboratory workup, EBV was detected by polymerase chain reaction on aqueous humor and scleral tissue analysis. The lesion subsided completely with systemic and local ganciclovir therapy. Subsequently, recurrent scleral nodule with iris plaque developed and was pathologically diagnosed as *Talaromyces marneffe*. The employed treatment, including intravenous amphotericin B and intracameral amphotericin B injection, was successful in attaining a significant regression of the lesion.

Clinical discussion: Although EBV treatment is debatable, our combination of systemic and local ganciclovir therapy demonstrated regression of EBV-caused scleral nodule and iris plaque. The organism's identification was complicated by *Talaromyces marneffe*, but it was easily treated.

Conclusions: In HIV-infected patients, EBV-associated sclerouveitis can be successfully treated with systemic and local ganciclovir therapy, and there is a possibility of coinfection with *Talaromyces marneffe*.

1. Introduction

With regard to uveitis, EBV has been found in inflamed eyes of patients with and without HIV infection. There has been controversy regarding EBV's pathogenic role and the need to treat it. A number of uveitis patients with proven EBV DNA have reported clinical improvement with systemic acyclovir therapy, the most commonly used treatment for EBV-associated uveitis, with or without intravitreal injection [1–3]. Besides acyclovir, nucleoside analogs with antiviral activity, such as ganciclovir and famciclovir, have shown moderate potency in suppressing virus replication during active diseases featured by acute or lytic replication of EBV [4–6]. However, amidst the controversy regarding the role of systemic acyclovir [7], there has been sparse reporting of intravenous ganciclovir treatment for EBV-associated uveitis. *Talaromyces marneffe* infection has long been linked to acquired immunodeficiency syndrome, which is caused by HIV infection. It can induce infectious keratitis and uveitis in the eye [8], but endophthalmitis is rare [9]. However, no case of EBV and *Talaromyces marneffe* coinfection in an immunocompromised patient has been reported.

Thus, we report a rare case of HIV infection with sclerouveitis caused by EBV and *Talaromyces marneffe*, which was successfully treated with a combination of ganciclovir and amphotericin B. This case report has been reported in line with the SCARE Criteria [10].

2. Case presentation

A 47-year-old HIV-positive female with a history of treated pulmonary tuberculosis presented, complaining of experiencing painful blurry vision in her left eye for 2 weeks. She had been treated with efavirenz, lamivudine, and tenofovir, and her CD4 count was 25 cells/mm³. Visual acuity of her right eye was no light perception for 2 months after she developed cytomegalovirus retinitis with rhegmatogenous retinal detachment in the right eye, and she refused curative surgery. At presentation, her best-corrected visual acuity (BCVA) in the left eye had decreased from 20/20 in the previous few months to 20/100. In the left eye, slit-lamp examination showed a whitish scleral nodule of 2.5 × 4.5 mm from 3 to 5 o'clock with dilated superficial episcleral vessels (Fig. 1A). There were 3+ anterior chamber cells and a vascularized

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tumor at the iris base from 3 to 5 o'clock. The vascularized tumor was covered with white plaque around 1.2×1.1 mm in size at the inferotemporal iris. The view of fundus of the left eye was hazy, however, with a flat retina. B-scan ultrasonography of the left eye demonstrated no vitritis. Presumptive diagnosis of infectious sclerouveitis was made, and laboratory workup was conducted. Treatment commenced with oral ciprofloxacin 500 mg twice a day and moxifloxacin 0.5% eye drops (every 2 h) followed by 1% prednisolone acetate eye drops (every hour).

Ten days later, visual acuity of her left eye dropped to counting fingers at 1 foot due to a cloudier cornea and 4+ anterior chamber cells with plasmoid aqueous. Her complete blood count showed mild microcytic hypochromic anemia and leukopenia while syphilis testing, toxoplasma serology, chest radiograph, and urine analysis were unremarkable. Aqueous humor was obtained and analyzed using the multiplex real-time PCR technique to detect viral pathogens (herpes virus family, adenovirus, human parechovirus, human enterovirus, mumps virus, and parvovirus B19) and real-time PCR was also used to identify *Mycobacterium tuberculosis* (MTB) complex genome. A few days after she had been hospitalized, the PCR result was positive only for EBV. As a result, she was diagnosed with EBV-associated sclerouveitis and received a 2-week course of 5 mg/kg intravenous ganciclovir twice daily with adjunctive intravitreal ganciclovir injections twice a week. During the first week of therapy, her condition remained stable, and an experienced uveitis specialist (S.S.) performed an incisional scleral biopsy. The pathological result showed granulomatous inflammation with negative staining for acid-fast bacilli (AFB), mucin, Gomori's methamine silver (GMS), Periodic-Acid-Schiff (PAS), Haematoxylin and eosin (H & E), and Epstein-Barr encoding region (EBER) in situ hybridization. However, scleral tissue analysis with PCR was positive for EBV but negative for MTB. The results of comprehensive microbiological study including gram staining, potassium hydroxide (KOH) preparation, acid-fast staining, mycobacterial cultures, and fungal cultures, were negative. As such, diagnosis of EBV-associated sclerouveitis was confirmed. During the second week of intravenous ganciclovir therapy with adjunctive

treatment of 2% ganciclovir eye drops (4 times/day) and 1% prednisolone acetate eye drops (8 times/day) to the left eye, her condition improved continuously (Fig. 1B). Ten days after the scleral biopsy, her left eye BCVA had improved to 20/63, and she was discharged with eye drops of ganciclovir, moxifloxacin, and prednisolone acetate.

One week after discharge, the scleral nodule on the inferotemporal side of the sclera increased in size, while the vascularized tumor had not relapsed (Fig. 1C); therefore, topical prednisolone acetate was decreased to four times daily, and ganciclovir eye drops were increased to one drop every 2 hours in the left eye. The regimen did not improve her condition, and iris neovascularization was present at 1-week follow-up. Rescue treatment, including intrascleral and intracameral ganciclovir injection together with intravitreal bevacizumab, was employed. After 2 weeks of the rescue treatment, iris plaque had relapsed and seclusio pupillae was observed while scleral lesion was stabilized by the treatment combination of ganciclovir, moxifloxacin, and prednisolone acetate eye drops.

She was hospitalized for the second operation including phacemulsification without intraocular lens implantation, and sclerouveal tissue biopsy in the left eye performed by an experienced uveitis specialist (S.S.). Intraoperatively, an oval window of exposed uveal tissue was observed after diseased sclera was removed (Fig. 1D), while the retina appeared normal. Sclerouveal tissue section stained with GMS and PAS demonstrated a yeast form organism with binary fission, which was morphologically compatible with *Talaromyces marneffei* (Fig. 2). PCR analysis showed that aqueous specimen was still positive for EBV; thus, diagnosis of EBV/fungus coinfecting sclerouveitis in the left eye was made. As recommended by infectious disease specialists, a 2-week course of intravenous amphotericin B in combination with intracameral amphotericin B injection was employed. Ten days after the treatment, a significant regression of iris plaque was observed, and exposed uveal tissue appeared healthy without recurrence of scleritis. Although a surgical option for scleral exploration with scleral patch graft was offered, the patient refused to proceed to surgery. Her BCVA was

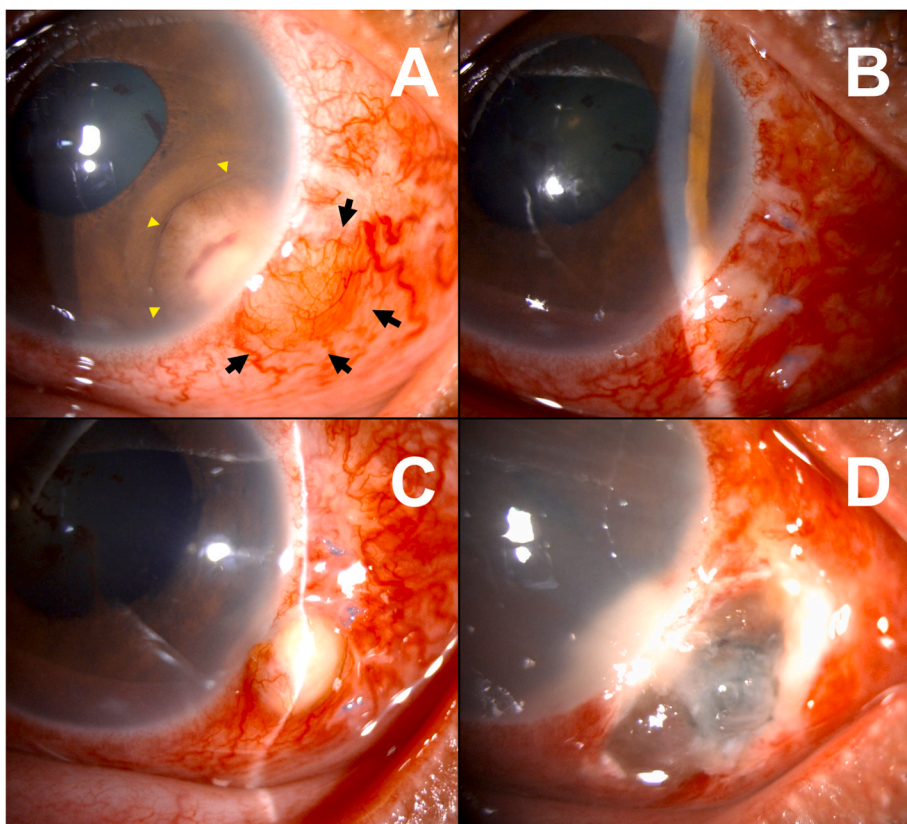


Fig. 1. Left eye: A) Slit-lamp photograph shows an inflamed, elevated scleral nodule in the inferotemporal part of the sclera (black arrow). An elevation of the peripheral iris covered with white plaque in the corresponding quadrant was obvious (yellow arrowhead). B) The resolution of the iris lesion and scleral nodule was demonstrated after a combination of systemic and local ganciclovir treatment. C) One week after discharge, a recurrence of scleral nodule was noted in the inferotemporal sclera. D) An oval window of exposed uveal tissue was noted after the second sclerouveal biopsy. There was a recurrence of whitish plaque on the iris in the corresponding quadrant before amphotericin B therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

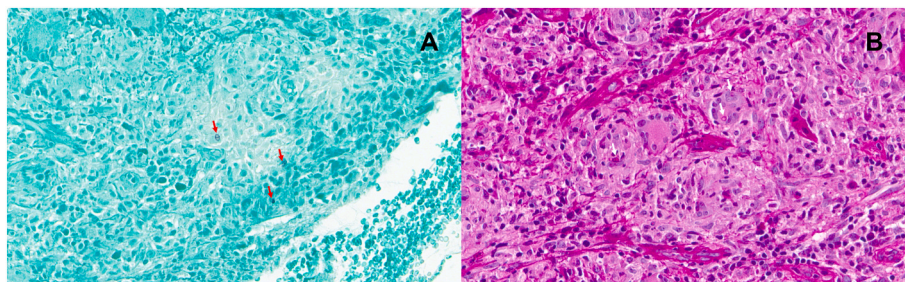


Fig. 2. Histopathological sections of the sclera in the left eye revealed chronic granulomatous inflammation. The characteristic binary fission within the yeast cell (arrows) can be seen by Gomori's methamine silver staining (A) and Periodic-Acid-Schiff staining (B). (magnification, $\times 40$).

hand movement due to cloudy cornea and aphakic condition. After the completion of intravenous amphotericin B, she was discharged from the hospital and lost to follow-up.

3. Discussion

The pathogenicity of EBV for uveitis is controversial for two reasons: 1) the difficulty in differentiating EBV latent infection from active lytic infection; and 2) the majority of EBV-associated intraocular inflammation co-exists with other pathogens which are more likely than EBV to be the culprits [11,12]. In our case, EBV was proven to be the only culprit by PCR analysis of the aqueous humor before *Talaromyces marneffeii* was later identified by pathological analysis. Acyclovir is the most commonly used antiviral treatment for EBV-associated uveitis; [1–3] however, its effectiveness for EBV-associated disease is still uncertain [7]. The beneficial role of ganciclovir therapy has been proven by an association with low or undetectable EBV DNA load [13], and there has been sparse reporting of the efficacy of ganciclovir treatment for EBV-associated uveitis. Our combination of systemic and local ganciclovir therapy appeared to cause the regression of scleral nodule and iris plaque.

Unfortunately, with her immune deficiency status, she later developed recurrent scleral nodule. The same extensive infectious workup including pathological investigation was conducted, and it was found that she was coinfecting with *Talaromyces marneffeii*. Although former pathological analysis failed to detect *Talaromyces marneffeii*, we believe that such organism may be present at the beginning. Shi and coworkers recently reported a similar case of iris tumor secondary to *Talaromyces Marneffeii* infection in a patient with AIDS. Next-generation sequencing identified *Talaromyces marneffeii*, and the PCR of fungus 26S rDNA was positive in the aqueous humor [14]. The patient's iris tumor and cutaneous lesions had subsided completely due to the combination therapy of oral voriconazole and fluconazole eye drops. Amphotericin B is a first-line agent for the initial treatment of talaromycosis [15]. Previous reports of cases with uveitis secondary to *Talaromyces marneffeii* have also demonstrated good response to the combined treatment, consisting of intravenous amphotericin and intraocular amphotericin injection [8, 16]. In our work, a 2-week course of intravenous amphotericin B in combination with intracameral amphotericin B injection rendered a significant regression of iris plaque. Nevertheless, there was still positive EBV DNA in the aqueous specimen, which was considered to be due to the remnants of dead virus due to the former resolution of the lesions.

In conclusion, a HIV-infected patient with sclerouveitis can be coinfecting with EBV and *Talaromyces marneffeii*. Systemic and local ganciclovir therapy were clinically effective for the treatment of EBV, while amphotericin B was the preferred treatment for *Talaromyces marneffeii*.

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preparation of the manuscript.

Ethical approval

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Rajavithi Hospital (approval No. 249/2564).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Sukhum Silpa-archa conceived the study, participated in design and coordination, data interpretation, drafted and edited the article. Sukhum Silpa-archa, Nitchamon Rangseechamrat and Wararee Sriyuttagrai participated in coordination and data collection. Sukhum Silpa-archa edited the article. All authors read and approved the final version of the article.

Research registration

Not applicable.

Guarantor

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.104283>.

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