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Detection of Leptospirosis Genome from the Aqueous Humor of a Patient with Bilateral Uveitis

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Abstract

Background.—Leptospira species are difficult to culture. Thus, when there is suspicion for an infectious etiology to uveitis, bacterial cultures may fail to identify Leptospira. We describe a case of leptospirosis-associated uveitis that evaded culture and molecular assays. DNA sequencing of the aqueous fluid showed the presence of Leptospira spp.

Methods.—Retrospective case review of clinical and laboratory features of a patient with ocular leptospirosis.

Results.—DNA sequencing identified the genome of Leptospirosis spp. in the aqueous.

Conclusion.—Metagenomic sequencing, by virtue of its unbiased nature, can be a helpful adjunctive test when a strong clinical suspicion for intraocular infection persists despite negative routine culture and molecular assays.

Keywords

leptospirosis; metagenomic sequencing; RNA sequencing; anterior chamber paracentesis; leptospirosis uveitis

Background

Leptospirosis-uveitis occurs most frequently in tropical climes. The constellation of acute course featuring non-granulomatous panuveitis with hypopyon, rapidly maturing cataract, vasculitis, optic disc edema, vitreous opacities has been suggested to have a high predictive

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value for the disease.[1] Suspicion for this spirochete can be raised, even outside of tropical areas, by a thorough review of travel history and exposures.

Objective

To demonstrate the utility of unbiased sequencing in a case of suspected infectious uveitis where cultures, polymerase chain reactions, and next generation 16S rRNA sequencing failed to identify a pathogen.

Case Report

A 33-year-old man was referred to the Proctor Foundation for bilateral chronic anterior and intermediate uveitis. He had previously worked as a tugboat captain and had no history of exposure to animals other than his dogs. His medical history was notable for multiple sclerosis. The patient underwent rituximab infusions, but when he failed to exhibit improvement in symptoms, he opted for treatment with autologous hematopoetic stem cell transplantation (HSCT) in Mexico. While in Mexico, the patient developed fevers and respiratory difficulty, which delayed HSCT. The patient's companions had similar symptoms. When HSCT proceeded, the patient noted that during his neutropenic phase (4 days following HSCT), he developed painless cloudy vision in the left eye without ocular redness, which was not evaluated. Four months later, the right eye developed similar symptoms. The patient was evaluated by a local ophthalmologist and was treated with high dose oral prednisone. When his vision continued to worsen, he returned to the United States for evaluation. Serology testing was negative for *Treponemal* antibody and interferon gamma release assay. Additionally, acid-fast culture of the serum for 6 weeks and routine bacterial and fungal cultures were negative. Because of a concern for an infectious etiology, three separate anterior chamber paracenteses were performed over one month, which were all negative for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and *Toxoplasma gondii* by polymerase chain reactions (PCR). His aqueous fluid exhibited no growth on bacterial and fungal cultures and was negative on next generation 16S rRNA sequencing performed in a CLIA-certified laboratory. MRI of brain and orbits showed no new demyelinating lesions.

On his presenting visit to the Proctor Foundation, his best-corrected Snellen visual acuity was 20/50 in the right eye and 20/20 in the left. Intraocular pressures were within normal limits and there was no afferent pupillary defect. There was iris heterochromia. Exam of the right eye revealed fine keratic precipitates (KPs) inferiorly, 4+ anterior chamber cell (Figure 1), pigment, no flare, 2+ anterior vitreous cells with snowballs, and a blunted foveal reflex. Exam of the left eye was notable for a quiet AC with extensive posterior synechiae, and 0.5+ anterior vitreous cells. Optical coherence tomography demonstrated cystoid macular edema (CME) in the right eye. Given his travel history and the high suspicion for an infection, we performed another anterior chamber paracentesis of the right eye, which was processed for DNA-seq as previously described.[2,3] DNA-sequencing identified *Leptospirosis santarosai* genomic material in his aqueous fluid (Figure 2). The patient's serum was subsequently sent to the US Centers for Disease Control (CDC) for confirmatory studies, which detected anti-*Leptospirosis* IgG antibodies. The patient was treated with oral doxycycline 100 mg

twice daily for 14 days. Due to persistent CME in the right eye, intravitreal dexamethasone implant (0.7 mg) was injected with resolution of the CME. The visual acuity in the right eye improved to 20/20 and the uveitis was inactive.

Discussion

Immunosuppression status increases one's susceptibility to systemic infections.[4] While bacterial infections have been noted to occur in those undergoing stem cell transplantation, the gram negative spirochete *Leptospirosis*, has not typically been encountered as a causative agent for patients evaluated in the United States.[4] Given the relatively widespread distribution of *Leptospirosis* in Mexico, the patient's stem cell transplantation and short-term residence in Mexico likely contributed to his susceptibility to this infection and development of uveitis.[5] This case illustrates the importance of a careful travel history intake and the potential benefit of unbiased testing for infectious etiologies when conventional diagnostics fail.

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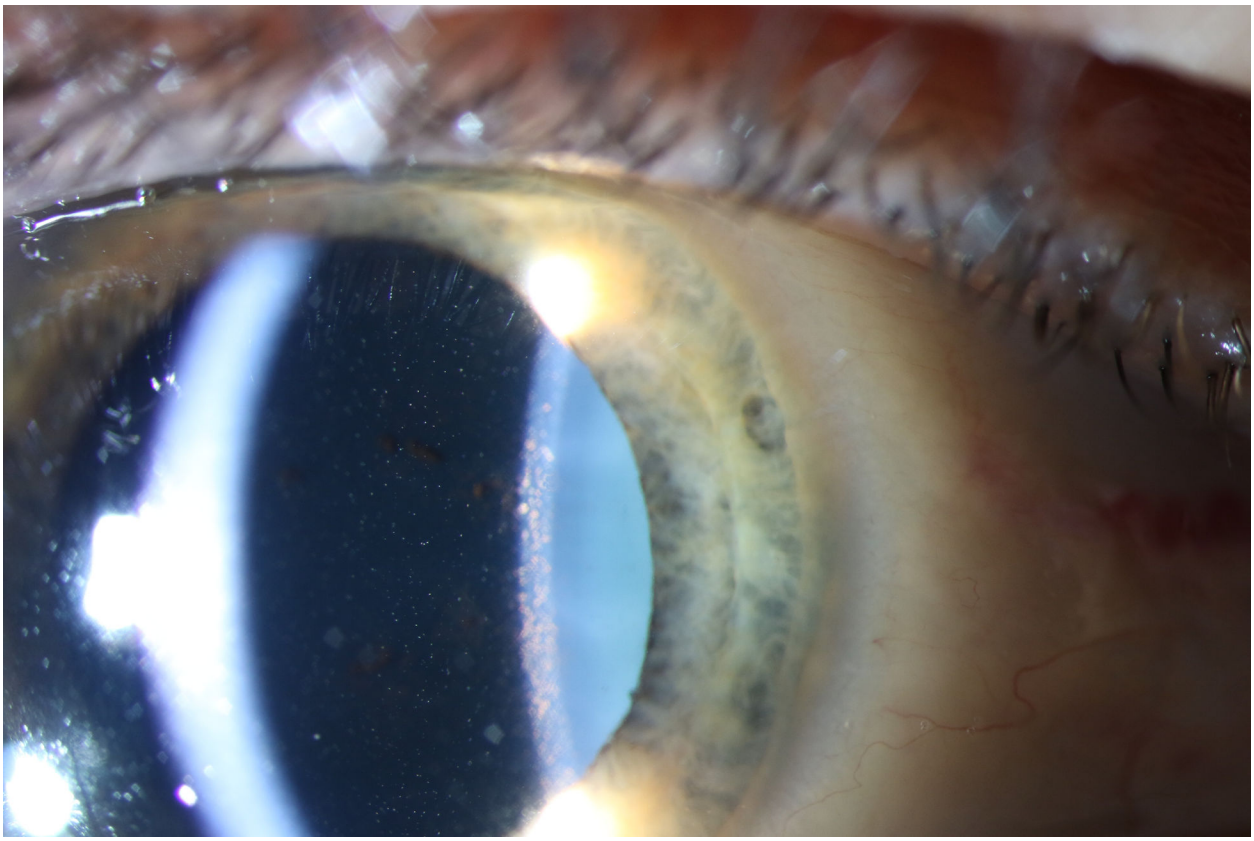

Figure 1.
Slit lamp photograph demonstrating robust anterior chamber cell in the right eye.

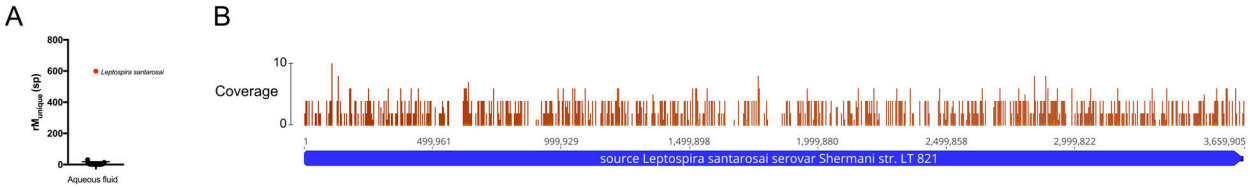

Figure 2.

A) Metagenomic deep sequencing results are shown as rM (reads per million reads) aligned at the species level. Red circles are the organisms determined to be pathogenic for the patient. Black circles are background. **B)** Sequencing reads from the patient's aqueous fluid were mapped to Leptospira santarosai genome reference database. Only chromosome 1 is shown.