Relapsing Uveitis due to Human T-lymphotropic Virus Type 1 in a Patient Living With HIV Diagnosed by Metagenomic Deep Sequencing

Varun K. Phadke,1,2,3 Jessica G. Shantha,3 and Ghazala O’Keefe1,2

1Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA, and 2Emory Eye Center, Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia, USA

HIV infection can result in vision loss from different causes, including HIV retinopathy and uveitis secondary to other infections, such as toxoplasmosis and viral retinitis. It is imperative to identify any infectious causes of uveitis to successfully treat the condition and prevent further vision loss. Metagenomic deep sequencing (MDS) is an emerging technology that presents an unbiased approach to the evaluation of clinical syndromes, including uveitis, that have not been diagnosed by pathogen-specific testing. Herein we present a case of a woman living with HIV with 11 years of relapsing bilateral uveitis refractory to systemic corticosteroid therapy who was diagnosed with human T-lymphotropic virus type 1 (HTLV-1)–associated uveitis by this technology. We also briefly review the literature of MDS as a diagnostic tool and the epidemiology, pathogenesis, and diagnosis of HTLV-1-associated uveitis.

Keywords. HIV; HTLV-1; uveitis; metagenomic deep sequencing.

CASE REPORT

A 54-year-old woman living with HIV presented to our clinic with recurrent uveitis. Fifteen years earlier, she was diagnosed with HIV infection and started on antiretroviral therapy. At the time of presentation, her CD4+ T-cell count was 300 cells/mm³ (18.4% CD4+ T cells) and the HIV viral load was undetectable (<20 copies/mL).

Eleven years before, she began experiencing episodic painless red eyes, initially in the left, then in both eyes, with associated floaters. These episodes initially occurred every 2–3 years and then increased in frequency. Her symptoms responded to topical corticosteroids, but 3 years before presentation to our institution, her symptoms became refractory to those agents. She had no history of ocular or sexually transmitted infections. She had no cat exposures. She had never received a blood transfusion or used injection drugs. She was born in the United States and had traveled briefly to Guyana and Costa Rica more than 10 years before the onset of her symptoms. She had no family history of eye or autoimmune disease or chronic infections.

During our initial evaluation, her best corrected visual acuity was 20/40 in the right eye and 20/250 in the left eye, with intraocular pressures of 21 mmHg and 31 mmHg, respectively. Anterior segment exam of the right eye was normal but revealed keratic precipitates and 4+ cells with flare in the left eye. Vitritis was present in the left eye, as were areas of vascular sheathing. Fluorescein angiography demonstrated peripheral capillary dropout (Figure 1). A workup for infectious and noninfectious causes of uveitis was unrevealing (Table 1). She was started on oral prednisone and improved. Unfortunately, she could not be weaned off systemic corticosteroids without a flare of her uveitis, and after 2 years she developed worsening vitritis in the left eye.

Given the absence of obvious risk factors for any specific infectious etiology of her uveitis, we sent ocular fluid for unbiased metagenomic deep sequencing (MDS) to the Proctor Foundation’s Ralph & Sophie Heintz Laboratory (University of California San Francisco [UCSF], San Francisco, CA, USA). The sample was sequenced under a research protocol that adhered to the tenets of the Declaration of Helsinki. The UCSF Institutional Review Board approved the study, and informed consent forms were obtained from the patient. MDS was performed as previously described [1–5]. Ocular fluid was strongly positive for human T-lymphotropic virus type 1 (HTLV-1). On subsequent questioning, the patient reported no obvious risk factors for HTLV-1 infection, including birth or residence in an endemic region, family history of HTLV-1 infection, or a history of blood transfusions, injection drug use, or sexual partners with known HTLV-1 infection; however, she did note that the partner from whom she contracted HIV was originally from Guyana, where HTLV-1 is endemic. The diagnosis of HTLV-1 infection was confirmed serologically by enzyme-linked immunosorbent assay and Western blot (positive bands for GD21, p19, p24, p26, p28, p32, p36, p53, gp46, and rgp46-I with a negative band for rgp46-II) and qualitative testing for HTLV-1 proviral DNA in plasma.

Her ocular disease is characterized by alternating episodes of vitritis requiring high-dose systemic corticosteroids to control, and she has since initiated azathioprine as a steroid-sparing...
immunosuppressant. Most recently, a dexamethasone intravitreal implant was used successfully to treat recurrent inflammation in her right eye, allowing her to be successfully weaned off systemic corticosteroids.

DISCUSSION

Metagenomic deep sequencing is an emerging technology that can assist in the diagnosis of clinical syndromes for which routine pathogen-directed workup is unrevealing [6]. In the workup of ocular inflammation, routine pathogen-specific diagnostics are often limited by the amount of fluid that can be sampled, low organism burden in the intraocular compartment, and limited availability of validated tests (specifically for HTLV-1) [7]. MDS overcomes these challenges by evaluating for viable and nonviable microorganisms in minute specimen volumes in an unbiased fashion. The potential application of MDS in diagnosing infectious uveitis has been previously described [1, 5]. MDS may be especially valuable in the evaluation of immunocompromised patients [8–12].

Uveitis in persons living with HIV may be due to a variety of infectious or noninfectious etiologies. Among individuals who achieve virologic suppression and immune reconstitution, the causes of uveitis parallel those seen in HIV-uninfected patients, and approximately one-third of cases remain idiopathic [13]. Here we described the use of MDS to establish HTLV-1 as the cause of uveitis, which was confirmed by serologic and virologic testing. HTLV-1-associated uveitis (HAU) is a distinct clinical manifestation

| Table 1. Diagnostic Evaluation of Bilateral Uveitis in Case Patient |
|---------------------------------------------------------------|
| **Diagnostic Test**                                      | **Result** | **Reference Range** |
| Infectious disease testing                                    |            |                    |
| Cytomegalovirus PCR of vitreous fluid                       | Negative   | Negative           |
| Varicella-zoster virus PCR of vitreous fluid                 | Negative   | Negative           |
| Toxoplasma gondii PCR of vitreous fluid                      | Negative   | Negative           |
| Rapid plasma reagin                                          | Nonreactive| Nonreactive        |
| Bartonella henselae IgM/IgG (positive for IgM, <1:64 for IgG) | Negative   | <1:64 IgG, <1:64 IgG |
| Borrelia burgdorferi EIA                                     | 0.13 LIV   | <0.99 LIV          |
| Noninfectious disease testing                                |            |                    |
| Erythrocyte sedimentation rate                               | 34 mm/h    | 0–30 mm/h          |
| C-reactive protein                                           | 0.87 mg/L  | 0.30–8.00 mg/L     |
| Anti-double-stranded DNA (dsDNA)                            | Negative   | Negative           |
| Extractable nuclear antibody (ENA)                          | Negative   | Negative           |
| Antineutrophil cytoplasmic antibodies (ANCA)                 | Negative   | Negative           |
| Rheumatoid factor                                            | <20 IU/mL  | 0–20 IU/mL         |
| Anticyclic citrullinated peptide antibody                    | 1.1 units/mL| ≤7 units/mL        |
| Angiotensin-converting enzyme                                | 28 U/L     | 9–67 U/L           |
| Human leukocyte antigen (HLA)–B27 typing                    | Negative   | N/A                |

Abbreviations: EIA, enzyme immunoassay; PCR, polymerase chain reaction.

*Quantiferon TB GOLD Plus.
of chronic HTLV-1 infection [14, 15]. It is a well-established cause of uveitis in parts of Japan where it is endemic [16], but in settings where seroprevalence is low, the burden of HTLV-1-related diseases is likely underappreciated.

The pathogenesis of HAU is thought to be immune-mediated, triggered by intraocular infiltration of HTLV-1-infected T cells, resulting in a local release of inflammatory cytokines [17]. Patients with HAU typically present with painless floaters and/or blurry vision, similar to the case patient. As observed in our patient, vitreous opacities are common fundoscopic findings, along with a mild retinal vasculitis, whereas chorioretinal lesions are usually absent [14]. Detection of proviral DNA in ocular fluid has been noted, but the diagnosis is usually made based on seropositivity for HTLV-1 and exclusion of other etiologies. Treatment options are limited and include either topical or systemic corticosteroids, but HAU has a propensity to relapse. Although some antiretrovirals have activity against HTLV-1, they have no proven role in the management of HAU. We were able to use intravitreal corticosteroids to successfully wean our patient off systemic corticosteroids.

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