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BRIEF REPORT

Symptomatic Acute Toxoplasmosis in Returning Travelers

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We report a family who acquired acute toxoplasmosis after a trip to Central America. One member developed severe clinical manifestations including bilateral chorioretinitis, hepatitis, and myocarditis requiring therapy. Symptomatic acute toxoplasmosis is unusual and possesses a diagnostic challenge. We discuss the clinical and epidemiological implications, laboratory diagnosis, and treatment plan.

Keywords. chorioretinitis; hepatitis; myocarditis; toxoplasmosis; travel.

CASE PRESENTATION

A family of 3—parents and a 1-year-old boy—residing in the United States traveled to Nicaragua for 10 days in the spring of 2017. During the trip, they had some casual contact with domesticated dogs, cats, and a parrot. They endorsed mosquito bites but did not see any ticks or swim in rivers or lakes. They ate pork the evening before departure (mother ate more than father; child ate a small amount). They did not recall seeing any rodents. Four days after returning to the United States, the 29-year-old mother developed retro-orbital headaches, fever, chills, body aches, and rash. Twelve days later, her fever persisted—up to 40°C—and she noticed cervical lymphadenopathy, nausea, and night sweats. Initial evaluation revealed a temperature of 38.6°C, mild transaminitis (ALT: 103/AST: 30), anemia, and lymphocytosis. She was not pregnant. Serologies for Zika, Chikungunya, Dengue, and Epstein-Barr virus came back negative. Stool and blood cultures were negative. Monospot and HIV tests were negative. She received intravenous ceftriaxone for 7 days, followed by ciprofloxacin for 3 days for presumed typhoid fever. One month into her illness, she continued with low-grade fevers, fatigue, new onset of blurry vision, and cervical lymphadenopathy (Figure 1A). Finally, we evaluated her in our travel clinic (at the University of Colorado Denver, School of Medicine) and ordered an additional work-up including serologies for *Toxoplasma gondii*. Her toxoplasmosis IgG was positive, and her IgM titer was >160 AU/mL at the ARUP laboratory. Confirmatory toxoplasma serology laboratory at the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory came back with toxoplasma IgG (Dye test) of 1:2048 (positive ≥ 1:16), IgM enzyme-linked immunosorbent assay (ELISA) of 10.9 (positive ≥ 2.0), IgA ELISA of 10.7 (positive ≥ 2.1), IgE ELISA >14.0 (positive ≥ 1.9), differential agglutination of 1600/1600 (acute pattern), and an IgG avidity test of 1.1 (low < 20.0), suggesting a recently acquired infection within 1–2 months. An ophthalmologic evaluation revealed bilateral focal inner retinal thickening with overlying vitritis, peripheral perivascular leakage, and focal autofluorescent retinal lesion (Figure 1D and E). Findings were consistent with bilateral retinitis. Her echocardiogram (ECG) showed right ventricular conduction delay and nonspecific T wave abnormalities (Figure 1C). Troponin I was mildly elevated at 0.26 ng/mL (0.00–0.05), but ECG was within normal limits. We started therapy with trimethoprim-sulfamethoxazole (TMP-SMX) at 5 mg/kg TMP twice daily. She was intolerant to TMP-SMX due to marked nausea, and on the 10th day of therapy, we switched her to oral clindamycin (300 mg QID) without pyrimethamine. Ophthalmology treated her with a single 1-mg intravitreal clindamycin injection in the left eye and topical prednisone. Her symptoms gradually resolved. Eye exam confirmed resolution of the retinal lesions at follow-up. Her troponin normalized. She completed 8 weeks of therapy and continued regular ophthalmologic surveillance.

The 30-year-old father had nonspecific symptoms of body aches, fatigue, headaches, and bilateral conjunctival injection (Figure 1B). Initial evaluation showed a temperature of 37.7°C and transaminitis (ALT: 112/AST: 327). A similar (to the above) pertinent workup was negative. ARUP's toxoplasma IgM/IgG were positive. Confirmatory toxoplasma serology laboratory at the Palo Alto Medical Foundation came back with toxoplasma IgG (Dye test) of 1:8000 (positive ≥ 1:16), IgM ELISA of 11.1 (positive ≥ 2.0), IgA ELISA of 9.9 (positive ≥ 2.1), IgE ELISA >14.0 (positive ≥ 1.9), differential agglutination of 800/400 (acute pattern), and IgG avidity of 2.0 (low < 20.0). He had no evidence of heart or eye disease—normal ECG and ophthalmology assessment—although troponin I was mildly elevated at 0.1 ng/mL (0.00–0.05). Due to persistent systemic symptoms,

Received 8 October 2017; editorial decision 5 March 2018; accepted 8 March 2018.

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DOI: 10.1093/ofid/ofy058

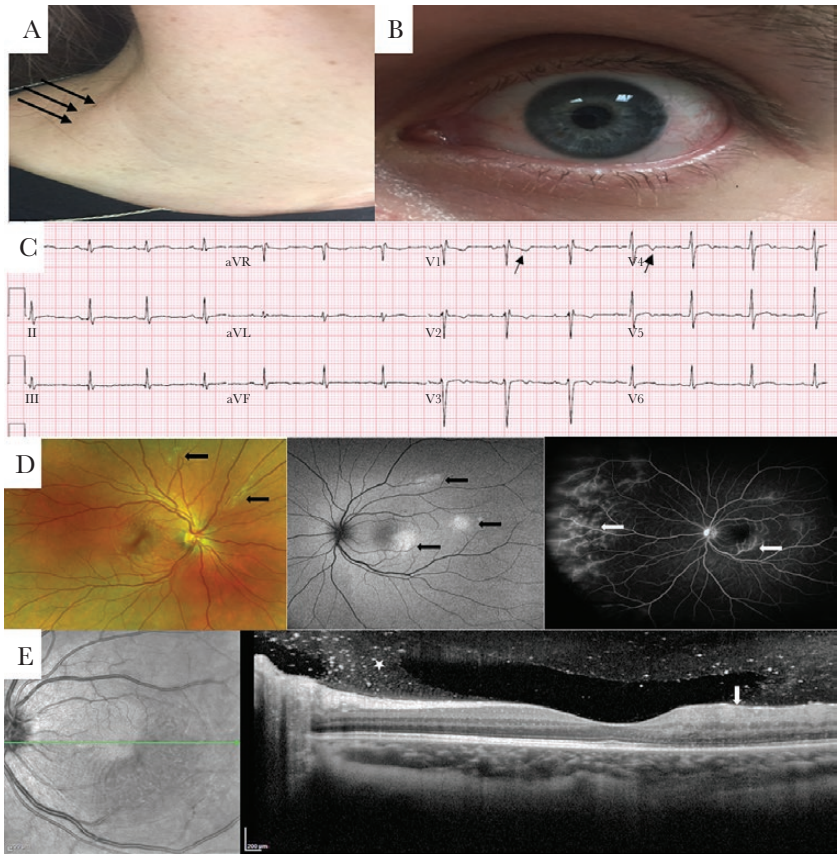

Figure 1. A, Neck anterior lymphadenopathy (black arrows). B, Mild conjunctival injection. C, RSR′ or QR pattern in V1 suggests right ventricular conduction delay and nonspecific T wave abnormality (black arrows). D, From left to right: color photograph of the right eye demonstrating 2 retinal infiltrates (black arrows); fundus auto-fluorescence of the left eye demonstrating 3 autofluorescent retinal infiltrates (black arrows); fluorescein angiogram of the left eye demonstrating retinal vascular leakage (white arrows). E, Spectral domain optical coherence tomography demonstrating inner retinal edema in an area of retinal infiltrate (white arrow) and vitreous cells (white star).

he received treatment with TMP-SMX and completed a 2-week course. His symptoms resolved completely.

The 1-year-old boy had a rash and nonspecific mild symptoms 28 days after return. Serology sent to Mayo showed a negative IgG and a positive IgM. Confirmatory toxoplasma serology laboratory at the Palo Alto Medical Foundation came back with toxoplasma IgG (Dye test) of 1:32 000 (positive ≥ 1:16), IgM ELISA of 10.0 (positive ≥ 2.0), IgA ELISA of 11.1 (positive ≥ 2.1), IgE ELISA of 11.9 (positive ≥ 1.9), and IgG avidity of 7.8 (low < 20.0). He had an eye exam and echocardiogram, both unremarkable. He was back to normal shortly and did not receive treatment.

DISCUSSION

We describe a family cluster disease of acute toxoplasmosis with evidence of hepatitis, myocarditis, and bilateral retinitis in 1 of them. The medical community under-reports acute toxoplasmosis. This phenomenon is in part because most infections being asymptomatic (~80%–90%) [1] but also because clinicians can easily overlook the acute presentation and it is not a reportable disease. Acute toxoplasmosis can be a significant source of morbidity; it causes fulminant myocarditis with heart failure, pneumonia, encephalitis, ocular disease, and congenital infection by vertical transmission—especially if acquired outside the United States [2, 3]. South America has reported deaths and severe clinical presentations with the disease including ocular toxoplasmosis [2, 4]. The pathogenesis of severity during acute infection is not clear. Several factors might play a role: (A) the toxoplasma strain genotype virulence—observational outbreaks in South America linked atypical strains to severity during acute infection; (B) inoculum size; (C) infectious form of the parasite (cyst vs oocyst); (D) net state of immunosuppression; and (E) host genetic factors. Symptomatic acute toxoplasmosis presents more often with painless cervical lymphadenopathy—a key clinical finding to suspect disease in our case. However, pulmonary (with symptoms similar to those seen in patients with community-acquired pneumonia) and ocular involvement with pneumonia seems to be present in some cases [5–7]. Published cases rarely report fulminant myocarditis or hepatitis [8]. Travelers to highly endemic areas for toxoplasmosis inadvertently expose themselves to the parasite. Diagnosis on their return home possesses a clinical challenge due to its atypical manifestations and lack of awareness among medical care providers. Case series from returning travelers

with toxoplasmosis have focused on mononucleosis-like illness caused by this infection, but severe manifestations of acute toxoplasmosis after travel have received less attention [9].

Serological testing remains the gold standard for diagnosis of acute toxoplasmosis. However, toxoplasma IgM testing—a classic marker for acute infection—can have a significant number of false-positive results and may remain positive for years after acute infection [10]. Therefore, for any positive toxoplasma IgM serum sample, we recommend submission of samples to a reference laboratory. In addition to IgM, IgA, IgE, differential agglutination, and IgG avidity can narrow the window of infection acquisition. If highly positive for IgA and IgE, an acute pattern for AC/HS and very low for IgG avidity, the patient most likely acquired the infection during the 2 months prior to serum sampling. Most clinicians would support that antitoxoplasma treatment is not indicated for immunocompetent patients with acute toxoplasmosis if asymptomatic or with mild self-limited symptoms. The presence of end organ injury or marked systemic symptoms is an indication for treatment. The first line of therapy for acute toxoplasmosis in immunocompetent patients consists of pyrimethamine plus sulfadiazine plus folinic acid. TMP-SMX, clindamycin, and atovaquone are alternative regimens. Due to comparable efficacy [11], the markedly increased cost of pyrimethamine, and lower dosing frequency, we chose TMP-SMXL as our first option. No clear evidence exists to support the routine use of antibiotics or steroids in isolated ocular toxoplasmosis. Decision to treat isolated ocular toxoplasmosis depends on the presence of iritis, vitritis, or chorioretinitis with lesions located within the vascular arcades or adjacent to the optic disk, size (>2 optic disc diameters), atypical presentation, or infection with South or Central America strains [12, 13]. In patients with ocular involvement, a high relapse rate of disease during the first year has been observed. TMP-SMX has been reported to reduce recurrences (0% vs 13% for 12 months' follow-up) [14], and we recommend its use in patients with ocular involvement. Unfortunately, in patients who are intolerant or allergic to sulfa drugs, there are no well-studied alternative options for prophylaxis. We advise frequent regular eye exam surveillance in this setting for at least 1 year. Toxoplasmosis remains an important diagnostic consideration among travelers with acute illness and can be a source of morbidity and disability. Clinicians require a high index of suspicions to decrease the associated complications.

Acknowledgments

We gratefully acknowledge the patients who provided with the images for this report. Written consent was obtained for the displayed photos.

Disclosure. No funding agencies had any role in the preparation, review, or approval of this manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the University of Colorado Denver or Stanford University.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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