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Seronegative ocular toxoplasma panuveitis in an immunocompetent patient

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ABSTRACT

Purpose: Toxoplasma gondii is the most common cause of infectious posterior uveitis worldwide in immunocompetent patients. Despite its prevalence, diagnosis can still be challenging and vision-threatening in cases with atypical presentations. This case exemplifies the importance of clinical exam and additional workup when required despite negative initial serology results.

Observations: A 73-year-old immunocompetent woman presented with a 2-year history of recurrent panuveitis and retinal necrosis not responsive to systemic antiviral therapy. Toxoplasma serum antibodies (IgG and IgM) were not detected on systemic workup one year prior. The slit-lamp exam revealed mutton fat keratic precipitates, panuveitis, and necrotic retinal lesions adjacent to a retinal scar. Repeated Toxoplasma serum antibodies (IgG and IgM) were again negative. However, aqueous fluid testing by polymerase chain reaction (PCR) was highly positive for Toxoplasma gondii. The patient improved after starting systemic anti-toxoplasma therapy.

Conclusion/Importance: To our knowledge, this is the first report in the literature of an immunocompetent patient with ocular toxoplasmosis and undetectable serum IgG and IgM. Aqueous fluid PCR testing is useful in suspected ocular toxoplasmosis in patients with vision-threatening lesions despite negative serology.

1. Introduction

Toxoplasmosis is the leading cause of infectious posterior uveitis in immunocompetent patients.[1] Ocular toxoplasmosis is the most common clinical manifestation of toxoplasmosis in an immunocompetent host.[2] The clinical diagnosis is generally deemed sufficient in typical presentations. Complimentary workup can be helpful in atypical cases, which includes serum serology (IgG and IgM), ocular serology via Goldmann-Witmer coefficient (GWC, the ratio of ocular to serum antibody converted into a coefficient, a ratio > 3 is considered diagnostic), and polymerase chain reaction (PCR).[3,4] Serum serology has been widely used for the diagnosis of toxoplasmosis in both immunocompetent and immunocompromised patients. Seronegative ocular toxoplasmosis has been reported in immunocompromised patients.[8,9] However, negative serum serology (both IgG and IgM) is widely accepted as adequate for ruling out infection in immunocompetent patients.[5] This case describes the presentation of an immunocompetent patient with seronegative ocular toxoplasmosis.

2. Case report

A 73-year-old woman presented for recurrent acute retinal necrosis (ARN) flare-up of the right eye (OD). Her medical history included type 2 diabetes mellitus, hypertension, dyslipidemia, deep venous thrombosis, hysterectomy, and chronic kidney disease. She had a 2-year history of waxing-and-waning ARN OD managed by oral valganciclovir 1 g three times daily (TID) during acute flares, and 1 g daily (QD) maintenance dose. Human Immunodeficiency Virus (HIV) screen and Toxoplasma serum antibodies (IgG and IgM) using chemiluminescence immunoassays (CLIA) (Access Toxo IgM II, Access Toxo IgG, Beckman Coulter Inc, USA) were negative one year prior, thereby ocular toxoplasmosis was excluded then.

On clinical exam, visual acuity (VA) was hand motion (HM) OD and 20/25 in the left eye (OS). Intraocular pressure (IOP) was 41 mmHg OD and 17 mmHg OS. Slit-lamp exam OD revealed mutton fat keratic precipitates (KPs), 2+ cells in the anterior chamber (AC), posterior chamber intraocular lens (PCIOL) deposits, vitritis, and an inferior macula yellowish lesion next to a temporal retinal scar [Fig. 1A]. Otherwise, a PCIOL was noted OS.

An AC tap was done in the office, followed by hospital admission for treatment with intravenous (IV) acyclovir and trimethoprim-sulfamethoxazole (TMP-SMX). We switched topical difluprednate four times daily (QID) to prednisolone acetate 1% drops QID and started cyclopentolate twice daily (BID). The aqueous fluid sample was sent for

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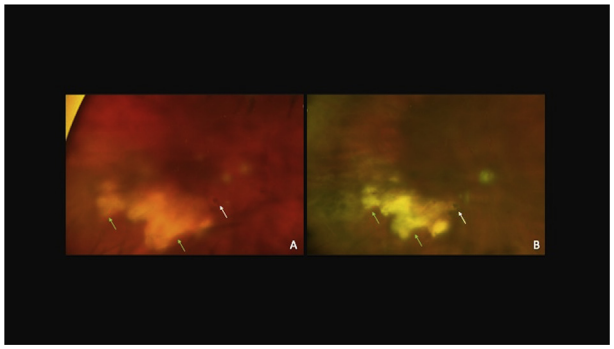

Fig. 1. Ultrawide field pseudo-color images showing the right eye on presentation with hazy media and retinal yellowish lesion inferio-temporally (green arrows) adjacent to a chorioretinal scar (white arrow) **(A).** The right eye one month after hospital discharge showing decreased media haze and regressing retinal lesion (green arrows) and older chorioretinal scar (white arrow) **(B).** (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), and Toxoplasma polymerase chain reaction (PCR) testing. Additionally, aerobic and anaerobic cultures were done. Toxoplasmosis serum IgG and IgM were tested using CLIAs on hospital admission and, once again, returned negative. As a result, IV TMP-SMX was stopped. Three days later, Toxoplasma PCR returned at 33,400 copies/mL. The sample was negative for HSV, VZV, CMV, and the cultures were unrevealing. As a result, IV acyclovir was stopped, and IV TMP-SMX was restarted. Immunological workup, including total serum immunoglobulins and lymphocyte subtypes with CD4 cell counts, was normal. Topical brimonidine, dorzolamide, timolol, and latanoprost were added for IOP control.

On hospital admission day 8, the patient developed hyponatremia secondary to the 5% dextrose component of IV TMP-SMX requiring treatment with hypertonic saline. She was switched to pyrimethamine, sulfadiazine, and leucovorin instead. At one month follow up, she reported improvement, with HM vision OD, IOP at 22 mmHg, resolving KPs, quite AC, decreased vitritis, and healing chorioretinal lesion (Figs. 1 and 2).

3. Discussion

The diagnosis of ocular toxoplasmosis can be challenging. Clinical exam, serology testing, and PCR are frequently used to diagnose suspected ocular toxoplasmosis.[3] Ocular serology via GWC testing has been reported to have a sensitivity of 93% and a specificity of 100%.[10] Serum IgG titer sensitivity and specificity varies depending on the threshold limit used for diagnosis (a threshold limit of > 40 IU/ml has a sensitivity of 85.4% and a specificity of 42.3%, and a threshold limit of > 250 IU/ml has a sensitivity of 45.1% and a specificity of 80.4%).[6] Serum IgM titer has a sensitivity of 99.4% and a specificity of 49.2% for Toxoplasma infections in general (non-specific to ocular involvement).[11] Ocular fluid PCR sensitivity ranges from 30% to 67%, while specificity is 100%.[12] PCR has been shown to be less sensitive in immunocompetent patients compared to immunocompromised patients, which is speculated to be due to a lower viral load.[4,12]

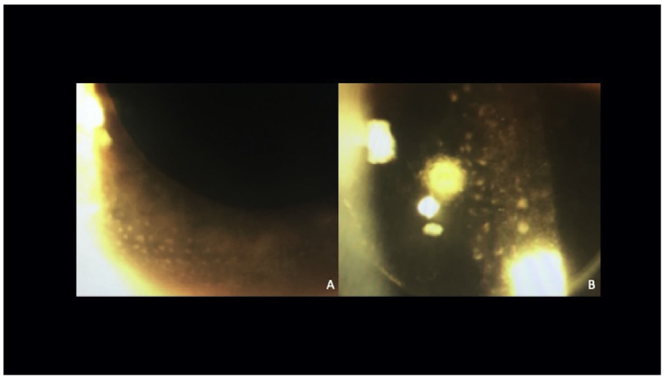

Fig. 2. Slit-lamp images of the right eye one month after hospital discharge showing decreased inferior keratic precipitates **(A),** and resolving inflammatory fibrin deposits on the lens' posterior surface **(B).**

Serology is commonly done using enzyme immunoassay (CLIA and enzyme-linked immunosorbent assay (ELISA)), immunofluorescence, or Sabin-Feldman dye test with live Toxoplasma gondii tachyzoites.[3,13] The Sabin-Feldman dye test is considered the classic gold standard serology test, but it is not frequently used because of the associated risk of laboratory-acquired infection during organism handling.[3,13] Enzyme immunoassays are more sensitive than immunofluorescence, with CLIA having higher sensitivity compared to ELISA.[13,14] Serum IgM negativity is less helpful in ruling-out ocular toxoplasmosis infection due to the majority of cases being a result of recurrence rather than initial infection.[7] Serum IgG, on the other hand, is expected to peak within eight weeks of primary infection and generally persists for life.[7] Our patient had the test performed twice, 12 months apart. In addition, she had normal total immunoglobulins, and lymphocyte subtype counts. These lab tests findings were discussed with the infectious disease team. Aqueous production of Toxoplasma IgG was not measured since the PCR result was diagnostic. A selective cellular immune defect that hinders antibodies production against Toxoplasma in this patient is a possibility that we cannot rule out.

Treatment is recommended when the infection is vision-threatening. The higher cost of pyrimethamine may promote treatment with TMP-SMX.[15] Close monitoring is needed with IV TMP-SMX in patients with kidney disease like our patient.

4. Conclusion

To the best of our knowledge, this is the first report in the English literature of PCR positive ocular toxoplasmosis and negative serum antibodies (IgG and IgM) in an immunocompetent patient. Aqueous fluid PCR testing is useful in suspected ocular toxoplasmosis patients with vision-threatening lesion despite undetectable serum immunoglobulins.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient. Institutional review board approves this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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