Implications of False Positive Serology of *Toxoplasma gondii* in a Pre-transplant Patient

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**CLINICAL HISTORY**

**Patient:** A 21-year-old white male with cystic fibrosis.

**Chief Complaint:** Pre-transplant workup in preparation for bilateral lung transplant.

**Past Medical History:** Cystic fibrosis diagnosed at age 3, onset of insulin-dependent diabetes around age 20, and multiple hospitalizations for pulmonary and gastrointestinal complications.

**Family and Social History:** The patient lives with his father and stepmother, has a pet bearded dragon, and has multiple tattoos and piercings. His stepmother has a cat, but he does not clean the litter box.

**Principal Laboratory Findings:** The pre-transplant workup included several tests for infectious diseases, tests of organ function, radiology studies, and markers of malignancy. The only significant finding was a positive *Toxoplasma gondii* (*T. gondii*) IgM titer (≥1:40) (reference values for IgM: negative; <1:40, positive; ≥1:40) and IgG (1:2048) (reference values for IgG: negative; < 1:16, equivocal; ≥1:16 - <1:256, positive; ≥1:256). Testing was done by indirect immunofluorescence assay (IFA) in April 2012 in our hospital laboratory. The patient was treated with sulfadiazine, leucovorin, and pyrimethamine. Three months later (July), he returned for follow-up testing. Real-time polymerase chain reaction (PCR) for *T. gondii* DNA performed by a reference laboratory was negative. One month later (August), Toxoplasma serology was performed by enzyme-linked immunosorbent assay (ELISA) by a different reference laboratory and showed an elevated IgM of 0.95 IU/mL (reference values: negative; <0.55 IU/mL, equivocal; ≥ 0.55 – < 0.65 IU/mL, positive; ≥ 0.65 IU/mL) and a normal level of IgG (<4 IU/mL). At this time, PCR was repeated and was negative. An additional month later (September), the patient’s serology studies were performed at a third reference laboratory and showed an elevated IgM of 1.32 IU/mL (reference values: negative; 0.89, equivocal; 0.90 – 1.09, positive; >1.10) and a normal IgG.

**Keywords:** *Toxoplasma gondii*, false positive IgM, serology

**Questions**

1. Based on *T. gondii* serology results, does the patient have *T. gondii* infection?
2. What is the possible etiology for false positive serology of *T. gondii*?
3. What is the recommended algorithm for testing serology of *T. gondii*?
4. What is the risk of toxoplasmosis in transplant patients?
5. What are the implications of reporting false positive *Toxoplasma* serology?

**Possible Answers**

1. *T. gondii* is an intracellular protozoan parasite. Most infections are transmitted via ingestion of oocysts in undercooked meat or contaminated water. Additionally, the parasite can be congenitally acquired transplacentally if a woman is primarily infected during pregnancy. Primary infections are usually asymptomatic, but can present as lymphadenopathy or a mononucleosis-like illness.

Diagnosis of toxoplasmosis is usually made by detection of Toxoplasma-specific IgG and IgM antibodies. Several tests are available to detect these antibodies within several weeks of infection including the Sabin-Feldman dye test, indirect immunofluorescent assay (IFA), agglutination, and ELISA. In addition, there are various real-time PCR assays with different sensitivities and specificities that can be used to supplement serology tests if the interpretation is difficult or for immunocompromised patients who fail to produce enough antibodies.

The patient was initially treated for possible toxoplasmosis based on positive serology (IgM and IgG) that was
performed by IFA. All subsequent testing by ELISA showed mild elevation of IgM and negative IgG. Due to a lack of specificity of immunofluorescent testing and the subjective interpretation of results, it is unlikely that the IgG result was a true positive. This conclusion is supported by the negative IgG in all subsequent tests performed by different reference laboratories. False negative results due to high titers of IgG (prozone phenomenon) were excluded by testing multiple dilutions in 2 different laboratories. The original specimen was not available for repeat testing and all subsequent specimens were sent to reference laboratories since serology services had been discontinued in our hospital laboratory. Typically, IgG antibodies appear within 1 to 2 weeks of infection, peak within 1 to 2 months, decline at variable rates, and persist for life.\(^1,2\)

In this case, the IgM was mildly elevated in all of the specimens. Since the IgG and DNA PCR were negative and the patient lacked any clinical manifestations of toxoplasmosis, it is likely that the IgM result was a false positive. IgM titers become negative within a few months after an acute infection. However, in some patients, positive IgM titers persist for 1 year or even longer.\(^1\)

2. The false positive rate of \(T. gondii\) IgM testing can be as high as 60%.\(^3\) The high sensitivity and negative predictive value of this assay, however, make it a good test to exclude toxoplasmosis when the result is negative. False-positive IgM can be caused by autoimmune antibodies including rheumatoid factor and antinuclear antibodies, acute viral infection, and non-specific in vitro binding.\(^3\) Serology testing for \(Toxoplasma\) IgM may be difficult to interpret, especially in immunocompromised patients and in patients who do not display signs or symptoms of the infection. The specific reason for the false-positive IgM in this patient could not be determined. In 1997, the Food and Drug Administration issued an advisory concerning the limitations of \(T. gondii\) testing.\(^4\)

3. Patients undergoing solid organ or bone marrow transplantation are at risk for reactivated or acquired toxoplasmosis; therefore, they should have pre-transplant testing for IgG antibodies (Figure 1). According to Centers for Disease Control and Prevention and the Clinical and Laboratory Standards Institute, a positive IgG and a negative IgM indicates past infection, while a positive IgM with a negative IgG may indicate a false positive IgM or an acute infection. In this scenario, if repeat testing...
in 2-3 weeks remains positive for IgG, acute infection is suspected, but if IgG is still negative, false positive IgM is more likely.\textsuperscript{5,6} If testing is performed in local laboratories, specimens should be submitted to a reference laboratory for confirmation. IgG avidity testing to distinguish recent from past infections and \textit{T. gondii} DNA PCR may be necessary in some situations.

4. In transplant patients, severe or disseminated toxoplasmosis can result either from a reactivation of latent infection in the recipient or infection from a cyst-containing organ from the donor.\textsuperscript{1} Reactivation of chronic infection may occur in the recipient regardless of the type of the allograft (D–/R+ or D+/R+), but the risk is closely related to the type and duration of immunosuppression and it is higher in patients receiving hematopoietic stem cell or liver transplants.\textsuperscript{1,2} A seropositive donor (D+) and seronegative recipient (R–) represent the highest risk for disease in heart, lung, heart and lung combined, and kidney transplant recipients.\textsuperscript{1,2} Trimethoprim/sulfamethoxazole prophylaxis is highly effective in these patients. Recipients in D–/R+, D+/R+, or D+/R+ scenarios rarely develop toxoplasmosis.\textsuperscript{2}

5. Patients with false positive \textit{Toxoplasma} serology may undergo unnecessary and potentially dangerous treatment and procedures. This patient experienced significant consequences from the false positive lab results: entry to the lung transplant list was delayed, and the patient received unnecessary medications, gave away his pets, and underwent numerous additional laboratory studies and office visits. Before any intervention, healthcare professionals should follow the published guidelines for diagnosing toxoplasmosis and should confirm the results by a reference laboratory. \textit{LM}

**References**


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