A 62-Year-Old Male Heart Transplant Recipient With Progressive Hypoxia

A 62-year-old man with a history of ischemic cardiomyopathy underwent orthotopic heart transplantation. Before transplantation, he completed three monthly cycles of plasmapheresis, with administration of IV immunoglobulin (Ig) to reduce the level of preexisting human leukocyte antigen antibodies. On the day of transplant, he was determined to be IgG seropositive for cytomegalovirus and *Toxoplasma gondii*. The patient was induced with alemtuzumab and received tacrolimus and mycophenolate mofetil for immunosuppression. He recovered uneventfully in the early posttransplant course.

On postoperative day 19, the patient reported a new cough that produced yellow sputum and shortness of breath. Vital signs were notable for a temperature of 38°C and a room air saturation of 95% on 4 L/min of oxygen. Physical examination findings were normal except for crackles at the left lung base. There was no evidence of cytomegalovirus in a whole-blood polymerase chain reaction (PCR) assay. Cultures of expectorated sputum and blood were obtained, and the patient received antibiotic therapy for hospital-acquired pneumonia. A chest CT image from postoperative day 19 is shown in Figure 1A. His oxygen requirement slowly increased. Four days later, he reported myalgias and a headache. He was afebrile, with a heart rate of 116 beats/min, BP of 124/62 mm Hg, respiratory rate of 26 breaths/min, and an oxygen saturation of 94% on 15 L/min via face mask. A lung examination demonstrated diminished aeration in the left base. There were no meningeal signs; cardiovascular, skin, neurologic, and musculoskeletal examination results were normal. The WBC count was $7.2 \times 10^9$/L with 91% neutrophils. There was no growth in the previously obtained cultures.
The patient was intubated and underwent BAL for cultures and cytologic examination. Soon thereafter, he became hypotensive. In addition to hemodynamic goal-directed therapy, therapy with meropenem, vancomycin, and voriconazole was started. Immunosuppressive medications were withheld. An echocardiographic examination showed preserved cardiac function. A repeat chest CT image from postoperative day 23 is shown in Figure 1B. Results from a head CT scan were unremarkable. During the next 48 h, the patient developed an increased vasopressor requirement and worsening hypoxemia, such that veno-venous extracorporeal membrane oxygenation was instituted. He also developed profound disseminated intravascular coagulation, with a platelet count of $30 \times 10^9$/L and a prothrombin time of 102 s. Cytologic examination results from BAL are shown in Figure 2.
What is the diagnosis?

**Diagnosis:** Disseminated toxoplasmosis with pneumonia and septic shock

**Discussion**

*T gondii* is a protozoan parasite that infects people worldwide but typically causes the clinical disease of toxoplasmosis only in people who are immunocompromised. Many animals, including humans, can be infected by *T gondii* through ingestion of undercooked meat containing tissue cysts (bradyzoites) or through eating food or drinking water containing oocysts shed in the feces of cats, the definitive host. In most people who are immunocompetent, infection with *T gondii* is subclinical; the parasite is contained as dormant tissue cysts, predominantly within muscle and the brain. The prevalence of *T gondii* exposure in the United States is approximately 11%.

Infection in people who are immunocompromised often results from reactivation of latent disease, as seen in patients who receive hematopoietic stem cell transplants or in those with advanced HIV disease, and it commonly manifests as CNS disease with brain abscesses. Less common clinical presentations include pneumonitis, myocarditis, or chorioretinitis. Patients who receive solid organ transplants and who lack prior immunity to *T gondii* (IgG seronegative), however, are at particular risk of disseminated toxoplasmosis because the parasite can be transmitted in the transplanted organ. The highest risk occurs in those patients who receive transplants and who are *Toxoplasma* “mismatched” with the donor (the recipient is seronegative, while the donor is seropositive); untreated, 25% of such patients will develop clinical toxoplasmosis. In these patients, prophylaxis, most commonly with trimethoprim-sulfamethoxazole, will effectively prevent infection.

Serologic testing for the presence of antibodies can establish if a person has been exposed to *T gondii* but is less useful in establishing the presence of acute vs latent disease. In suspected acute toxoplasmosis, direct evidence of *T gondii* infection is essential and most often comes from either PCR amplification of *T gondii* DNA in blood or body fluids or from pathologic demonstration of the parasite. The Giemsa-stained BAL cytopsins showed numerous neutrophils with intracellular and extracellular crescent-shaped tachyzoites (the rapidly multiplying stage of *Toxoplasma*) (Figs 2A, 2B), which are consistent with *T gondii* organisms; this result was the first indication of toxoplasmosis in the patient. This finding was subsequently confirmed with a positive immunohistochemical stain for *Toxoplasma* performed on the BAL cell block (polyclonal rabbit antibody, dilution 1:50; Biogenex; San Ramon, California) (Fig 2D). Furthermore, the BAL and serum were submitted to the
Toxoplasma Serology Laboratory (Palo Alto, California) for real-time PCR amplification; *T gondii* DNA was detected from both samples, thus providing further evidence of active infection.

After the CNS, the lung is the organ most commonly affected by *T gondii* infection. Most *Toxoplasma* pneumonia occurs in patients who are immunocompromised; chest imaging typically shows diffuse interstitial infiltrates, although nodular infiltrates, consolidation, and pleural effusion, as seen in the patient, can occur. Toxoplasmosis resulting in septic shock and disseminated intravascular coagulation is rare. Mortality in patients who are immunocompromised and who have disseminated toxoplasmosis is high, with reported rates of ≤ 80%. Early treatment of disseminated toxoplasmosis improves outcomes. Pyrimethamine, a folic acid antagonist, is considered the most effective drug against *Toxoplasma* and is usually combined with either sulfadiazine or clindamycin in the treatment of acute disease. The most common side effect of pyrimethamine therapy is myelosuppression, which can be ameliorated by the administration of folinic acid.

**Clinical Course**

Review of the patient's transplant records revealed that although he was IgG positive for *T gondii* at the time of transplantation, he had a negative *T gondii* IgG serologic examination result 9 months prior. The donor was IgG seropositive for *T gondii*. The IV Ig the patient received prior to transplant likely resulted in transient levels of detectable *T gondii* antibodies. The patient, who had mild postoperative renal injury and who was felt to be at low risk for toxoplasmosis at the time of his transplant, was not receiving prophylactic therapy as an inpatient. Repeat serologic testing for the presence of *T gondii* IgG during his acute illness, approximately 30 days after the receipt of the IV Ig, was negative, supporting the hypothesis that his one detectable *T gondii* IgG level at the time of transplantation was due to the IV Ig. Although the patient was treated with appropriate therapy when toxoplasmosis was identified, he succumbed to overwhelming infection. No other infection was identified. An autopsy revealed disseminated *Toxoplasma* tachyzoites and, limited to the donor heart, bradyzoites (tissue cysts) (Fig 3), the source of his toxoplasmosis.

![Figure 3](image)

**Figure 3** Myocardium from donor heart demonstrating *Toxoplasma* bradyzoite (tissue cyst) (hematoxylin-eosin stain, original magnification × 1,000).

**Clinical Pearls**

1. **Patients who are immunocompromised, particularly recipients of solid-organ transplants who are *T gondii* seronegative, are at risk for toxoplasmosis and commonly present with symptoms of CNS or lung infection that can progress to septic shock.**

2. **The use of IV Ig in the peritransplant period confounds the interpretation of commonly used serologic examinations for opportunistic infections, including those for Toxoplasma; prior use of IV Ig should be kept in mind when assessing the risk of opportunistic infection and planning prophylactic regimens.**

3. **Direct evidence of *T gondii* infection is essential when acute toxoplasmosis is suspected. Tests that can be used include PCR for *T gondii* DNA from blood or body fluids or pathologic visualization of the organism in body fluids or tissues.**

4. **Disseminated toxoplasmosis in patients who are immunocompromised carries a high mortality. Early empirical**
therapy with a pyrimethamine-based regimen while diagnostic testing is ongoing may improve outcomes.

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SUGGESTED READINGS:


