Toxoplasma gondii Pneumonia in Immunocompetent Subjects: Case Report and Review

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Case report. A 41-year-old man was admitted to the emergency department of the Hospital do Servidor Público Estadual (São Paulo, Brazil) on 24 September 2005 with an 8-day history of fever, myalgia, and headache followed by 4 days of nausea and vomiting. He reported consumption of semiraw beef 20 days before developing symptoms. Although he denied a history of contact with sewage or flood water, he reported the presence of rats in his dwelling area. The patient reported no comorbidities or use of any medication prior to the presentation of symptoms.

A physical examination revealed fever (temperature, 40°C), jaundice (1 on a scale of 4), hepatosplenomegaly, and tachycardia (heart rate, 115 beats per min) but no lymph node enlargement. Hematological blood tests revealed a total WBC count of 2700 cells/mm³ (53% neutrophils and 43.2% lymphocytes with presence of atypical cells), a hemoglobin level of 11.6 g/dL, and a normal platelet count. Blood chemistry revealed hepatitis (aspartate aminotransferase level, 269 UI/mL; alanine aminotransferase level, 312 UI/mL), mild hyperbilirubinemia (total bilirubins, 2.32 mg/dL), and elevated lactic desidrogenase (755 U/L). Findings of an examination of a urine sample were unremarkable.

Thirty six hours after admission to the hospital, the patient developed respiratory insufficiency with bilateral pulmonary reticular opacities suggestive of interstitial infiltrate (figure 1).
and an arterial partial pressure of oxygen of 44.6 mmHg. He received intravenous penicillin, ceftriaxone, and clarithromycin, as well as noninvasive respiratory support. Serologic testing revealed the presence of *T. gondii*-specific IgM antibodies by ELISA. An HIV-1 antibody test had negative results. Blood cultures did not reveal any pathogen growth. An immunological analysis revealed 435 CD4+ T cells/µL and 1601 CD8+ T cells/µL (CD4+:CD8+ T cell ratio, 0.27), and immunoglobulin fractions were as follows: IgG, 1656 mg/dL; IgM, 1169 mg/dL; and IgA, 525 mg/dL. Treatment for acute *T. gondii* infection was initiated with sulfadiazine, pyrimethamine, corticosteroids, and folinic acid.

In the following 3 days, the patient’s respiratory insufficiency worsened, which was associated with a profound decrease in hemoglobin level (from 11.6 g/dL to 6.6 g/dL within 6 days) but without evidence of blood loss or hemolysis. He showed a marked improvement in clinical, radiological, and laboratory findings after the fourth day of therapy for *T. gondii*, and he was discharged from the hospital 12 days after admission. Toxoplasmosis treatment was maintained for 30 days.

Samples of blood, CSF, and sputum were assayed for *T. gondii* DNA after alkali extraction using PCR with B1 gene primers [6]. Despite normal cytological and chemistry findings, PCR revealed a typical 115–base pair product in the CSF sample. Parasite isolation was also attempted using peripheral blood Ficoll-Hypaque purifieduffy coat cells injected intraperitoneally in Balb/C mice, equivalent to 0.5 mL of blood per mouse. After 15 days of infection, analysis of peritoneal washing fluid samples of 2 of the 4 mice revealed typical tachyzoites, as shown in figure 1D. These washing samples were reentered into the mice and suggested a type III strain infection [7].

During the follow-up period, the patient experienced continued fever and myalgia that resolved 8 days after he was discharged from the hospital. Lymphocyte counts revealed 681 CD4+ T cells/µL and 921 CD8+ T cells/µL (CD4+:CD8+ T cell ratio, 0.74) after 1 month and 830 CD4+ T cells/µL and 1383 CD8+ T cells/µL (CD4+:CD8+ T cell ratio, 0.60) after 1 year of follow-up. Immunoglobulin fractions returned to normal values after 1 year (IgG, 1513 mg/dL; IgM, 87 mg/dL; and IgA, 202 mg/dL).

**Discussion.** *T. gondii* can invade every nucleated cell in the body, although the preferred target organs are the lymph nodes, brain, heart, and lungs. Proliferation of tachyzoites results in the infection of neighboring cells and necrosis, which can be associated with an intense mononuclear cell reaction [8]. In immunocompetent subjects, the infection is usually asymptomatic. In the CNS and in the eye, 2 immune privileged sites where antibody and complement levels are low [9, 10], ongoing tachyzoite destruction can occur, although resolution of infection has occurred in other tissues. After the period necessary for mononuclear cell activation and development of a specific immune response in an immunocompetent host, the infection is generally controlled, and tissue cysts are formed. Stably replicating tachyzoites are present in these cysts and may reactivate in the event of an immune deficiency.

As is true with a number of intracellular protozoan infections, IFN-γ is considered to be central in the generation of macrophages with antimicrobial activity that are responsible for parasitic control [11–13]; however, recent reports have described IFN-γ–independent pathways of immunological antimicrobial activity using TNF-α [14], CD40-CD154 signaling [15, 16], or IL-12 [17]. Many other defense mechanisms, such as nitric oxide generation, specific antibody production, and oxygen-dependent defense pathways, are essential, along with cellular activation, to control the parasite in its proliferative stage [8]. In vivo data reveal that reactive nitrogen intermediates are important for antimicrobial activity against intracellular pathogens [18], and nitric oxide synthase 2 is essential for *T. gondii* control in chronic-phase infection models [19].

Patients with AIDS have been shown to have a defect in the ability of T lymphocytes to produce appropriate antigen-specific IFN-γ [20], despite high circulating levels of total serum IFN-γ [21]. This production is inhibited in cases in which *T. gondii* is found in the lung (e.g., in patients with AIDS and in transplant recipients) [8]. This phenomenon is reflected by the high frequency of pulmonary involvement in HIV-infected sub-

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**Figure 1.** Sequential radiographs of the thorax showing mild bilateral interstitial infiltrate at the patient’s admission to the hospital (24 September 2005; A), marked heterogeneous bilateral opacity 4 days later (28 September 2005; B), and regression of lung involvement at a follow-up visit (26 October 2005; C). D, Phase-contrast microscopy of peritoneal washing samples obtained from mice 15 days after their injection with peripheral blood Ficoll-Hypaque purifieduffy coat cells from the patient, revealing typical extracellular live tachyzoites (original magnification, x1000).
<table>
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<tr>
<th>Patient</th>
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<th>Age (years, sex)</th>
<th>Country</th>
<th>Main clinical and laboratory findings</th>
<th>Consumption of raw or undercooked meat</th>
<th>Toxoplasmosis serological findings</th>
<th>Imaging findings</th>
<th>Parasitological diagnosis</th>
<th>Outcome</th>
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<tr>
<td>1</td>
<td>Pinkerton et al. [25]</td>
<td>1941</td>
<td>43 (F)</td>
<td>United States</td>
<td>Fever, rash</td>
<td>NR</td>
<td>NR</td>
<td>Pulmonary congestion</td>
<td>Necropsy: intracellular <em>T. gondii</em> in alveoli and bronchioles</td>
<td>Death</td>
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<td>2</td>
<td>Pinkerton et al. [25]</td>
<td>1941</td>
<td>50 (M)</td>
<td>United States</td>
<td>Fever, weakness, cough, dyspnea</td>
<td>NR</td>
<td>NR</td>
<td>Irregular areas of increased density</td>
<td>Necropsy: intracellular <em>T. gondii</em> in spleen and lungs</td>
<td>Death</td>
</tr>
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<td>3</td>
<td>Amato Neto et al. [26]</td>
<td>1969</td>
<td>28 (M)</td>
<td>Brazil</td>
<td>Fever, cough, headache, fatigue</td>
<td>NR</td>
<td>NR</td>
<td>BL interstitial infiltrates</td>
<td>Isolation of <em>T. gondii</em> during autopsy (from lungs, heart, and CNS)</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>Candolfi et al. [5]</td>
<td>1993</td>
<td>33 (F)</td>
<td>France</td>
<td>Fever, cough, dyspnea</td>
<td>NR</td>
<td>IgM positive and IgG positive</td>
<td>BL reticulonodular opacities</td>
<td>BAL fluid sample inoculated onto MRC-5 tissue cultures</td>
<td>Full recovery</td>
</tr>
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<td>5</td>
<td>Darde et al. [24]</td>
<td>1998</td>
<td>35 (M)</td>
<td>French Guyana</td>
<td>Fever, myalgia, lymph node enlargement</td>
<td>No</td>
<td>IgM positive and IgG positive</td>
<td>BL pulmonary infiltrates</td>
<td><em>T. gondii</em> trophozoites detected in BAL</td>
<td>Full recovery</td>
</tr>
<tr>
<td>6</td>
<td>Carme et al. [22]</td>
<td>2002</td>
<td>17 (M)</td>
<td>French Guyana</td>
<td>Fever, ELELs, pneumonia</td>
<td>Yes</td>
<td>IgM positive and IgG positive</td>
<td>BL alveolar infiltrates</td>
<td>Blood inoculation in mice and <em>T. gondii</em> isolation postinoculation</td>
<td>Full recovery</td>
</tr>
<tr>
<td>7</td>
<td>Carme et al. [22]</td>
<td>2002</td>
<td>22 (M)</td>
<td>French Guyana</td>
<td>Fever, ELELs, pneumonia</td>
<td>Yes</td>
<td>IgM positive and IgG positive</td>
<td>BL interstitial infiltrates</td>
<td>Blood inoculation in mice and <em>T. gondii</em> isolation postinoculation</td>
<td>Full recovery</td>
</tr>
<tr>
<td>8</td>
<td>Carme et al. [22]</td>
<td>2002</td>
<td>40 (M)</td>
<td>French Guyana</td>
<td>Fever, ELELs, pneumonia</td>
<td>No</td>
<td>IgM positive and IgG positive</td>
<td>BL interstitial infiltrates</td>
<td>Blood inoculation in mice and <em>T. gondii</em> isolation postinoculation</td>
<td>Full recovery</td>
</tr>
<tr>
<td>9</td>
<td>De Salvador-Guillouet et al. [23]</td>
<td>2005</td>
<td>19 (M)</td>
<td>France</td>
<td>Fever, cough, dyspnea, ELELs</td>
<td>NR</td>
<td>IgM positive and IgG positive</td>
<td>BL interstitial infiltrates</td>
<td><em>T. gondii</em> tachyzoites detected in BAL fluid sample</td>
<td>Full recovery</td>
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<td>10</td>
<td>Present case</td>
<td>2005</td>
<td>41 (M)</td>
<td>Brazil</td>
<td>Fever, fatigue, dyspnea</td>
<td>Yes</td>
<td>IgM positive and IgG positive</td>
<td>BL reticulonodular opacities</td>
<td><em>T. gondii</em> tachyzoites in mouse peritoneal washing sample after injection with patient’s peripheral blood Ficoll-Hyapque purifieduffy coat cells</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

**NOTE.**  BAL, bronchoalveolar lavage; BL, bilateral; ELEL, elevated liver enzyme level; NR, not reported.
jects with low CD4+ T cell counts who live in certain geographic areas. In a French study of pulmonary involvement in the pre-HAART era, a significant proportion of patients with AIDS received a diagnosis of Toxoplasma pneumonia [4]. Conversely, lung involvement associated with Toxoplasma infection is rather rare in immunocompetent subjects. We were able to identify only 9 cases of Toxoplasma pneumonia with parasitic confirmation in the medical literature. Table 1 summarizes the epidemiological, clinical, and diagnostic data from previous reports and from the present case. Although more cases have been published recently, Toxoplasma pneumonia has been recognized since the 1940s. Most patients were young men (male sex, 80%; median age, 34 years; interquartile range, 23.5–40.7 years). A common epidemiological feature, as suggested by several other cases with serological diagnosis and no parasite isolation, was the consumption of raw or undercooked meat (game) — a common practice in developing countries [22].

In addition to the respiratory clinical presentation, all patients had fever, and many reported nonspecific associated symptoms, such as myalgia, weakness, and rash. Elevated liver enzyme levels and imaging findings, mostly reflecting interstitial lung involvement, were often described. Since the 1990s, all patients have been positive for IgG and IgM Toxoplasma–specific antibodies. A parasitological diagnosis was made on the basis of tachyzoite isolation in bronchoalveolar lavage fluid, during mouse inoculation, or during necropsy. The outcome has dramatically changed from that of the 3 initially reported cases; all patients with cases reported in the last 2 decades experienced full recovery. This may be a consequence of the improvement in intensive care — in particular, the improvement in respiratory support.

No particular predisposing factors for Toxoplasma lung involvement in immunocompetent subjects have been described. It is possible, because of the very limited number of reported cases, that these individuals were infected with a high parasite burden or that they acquired the infection through a different route, such as inhalation (as has been suggested by others [23]). However, no case series or reports have established such an association. To date, no parasite strain has been shown to have specific pulmonary tropism, but there are some suggestions that South American strains — especially those from the Amazon — could be more virulent or aggressive, leading to severe disseminated disease [23, 24].

Clinical and image-based findings associated with pulmonary toxoplasmosis mimic those associated with many other atypical pneumonias, and pulmonary toxoplasmosis should be considered as a differential diagnosis; a risk of Toxoplasma infection from raw or undercooked meat consumption or other potential exposure must be investigated. Once suspected, a diagnosis of toxoplasmosis must be pursued through testing for serum IgM–specific antibodies and, ideally, through further investigation of biological samples (especially sputum samples) by cytological analysis, PCR, or bioassays for T. gondii. Specific antimicrobial therapy must be instituted in the advent of high suspicion because of the potentially life-threatening course of the disease and the potential for a complete recovery.

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References