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## Severe Toxoplasmosis in Immunocompetent Hosts: Be Aware of Atypical Strains

*To the Editor*:

*Toxoplasma gondii* is an intracellular protozoan parasite with a worldwide distribution. Humans are generally infected by consumption of undercooked meat or vegetables and water soiled by cat feces (1). Usually asymptomatic in healthy hosts, the primary infection leads to mononucleosis-like illness with cervical lymphadenopathy in 10% of subjects (2). Severe toxoplasmosis can be found in the immunocompromised population, particularly in patients with AIDS (3). In healthy individuals, this condition is rare in Europe and the United States but seems to be more common in tropical areas (4).

We present the case of a 47-year-old man referred to our institution for a flu-like syndrome with dyspnea that had not responded to oseltamivir and then ceftriaxone. Night sweats, nausea, and vomiting appeared after admission. Physical examination revealed evening fever of 38–39°C, thoracic macular rash, and enlarged supraclavicular and axillary and inguinal supracentimetric lymph nodes. Blood pressure was 115/75 mm Hg, mean heart rate was 90 beats per minute, respiratory rate was 20 breaths per minute, and transcutaneous oxygen saturation was 92% breathing ambient air. The pulmonary auscultation was normal. A chest radiograph showed subtle, diffuse, interstitial infiltrates (Figure 1A). Initial laboratory tests revealed a normal blood cell count. The arterial blood gas results on room air were: pH 7.52, $Pa_{O_2}$

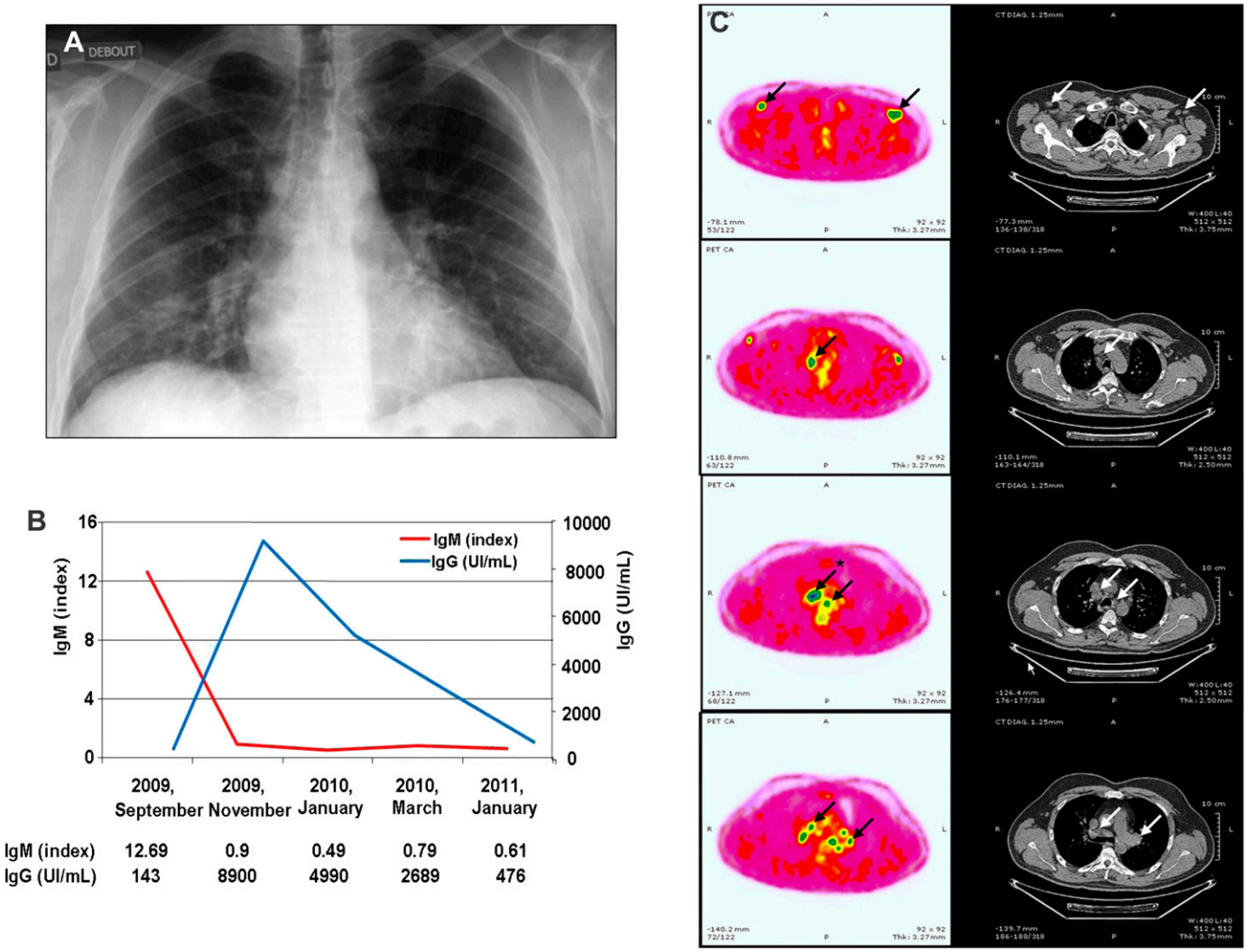


***Figure 1.*** (*A*) Chest radiograph revealed subtle diffuse interstitial infiltrates. (*B*) The *Toxoplasma gondii* serological status evolution suggested a recent primary infection: a rapid increase IgG was associated with decrease of specific IgM (IgG titers ⩾ 3 IU/ml and IgM index ⩾ 0.6 are considered positive; AxSYM system, Abbott Laboratories, Lake Forest, IL). (*C*) The 18-fluorodeoxyglucose PET/CT scan showed uptake in the peripheral and mediastinal lymphadenopathy (*arrows*). The standardized uptake values were: 4 g/ml in axillary and mediastinal adenopathy, except in the adenopathy marked with an *asterisk* (6.3 g/ml).

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60 mm Hg, $Pa_{CO_2}$ 30 mm Hg, $HCO_3^-$ 25 mEq/L, $Sa_{O_2}$ 91%. Hepatic function tests were: bilirubin 0.4 mg/dl (normal value [N]), alanine transaminase 185 U/L (4N), aspartate transaminase 130 U/L (3.5N), alkaline phosphatase 439 IU/L (1.5N), γ–glutamyl transferase 351 U/L (5.5N), and lactate dehydrogenase 837 IU/L (2N). The blood C-reactive protein level was 20 mg/L. On the third day of admission, a mononucleosis-like syndrome appeared on the complete blood count (leukocytes: $8 \times 10^9$/L; lymphocytes: $4.9 \times 10^9$/L [61%], 13% of which were hyperbasophilic lymphocytes). Blood cultures, *Legionella* antigenuria, and serological testing results for HIV, cytomegalovirus, hepatitis A, B, and C viruses, and *Mycoplasma pneumoniae* were negative and consistent with past infection for Epstein-Barr virus and *Chlamydia pneumoniae*.

*T. gondii* serology was then performed and compatible with a recent infection (Figure 1B). At this stage, a thoracic high-resolution computerized tomography (CT) scan showed mediastinal lymphadenopathy but no more parenchymal infiltrate. The patient underwent bronchoscopy with bronchoalveolar lavage (BAL). Direct microscopic examination, bacterial and fungal cultures of the BAL fluid sample were negative, but a real-time polymerase chain reaction–based assay detected DNA of *T. gondii*. Immunoglobulin serum levels and B- and T-cell phenotypes were all normal. Treatment with spiramycin (9,000,000 IU/d) was initiated 12 days after admission (20 d into the illness) and improved the symptoms with defervescence on the third day. The patient was discharged and the treatment was continued for 3 weeks.

One month later, clinical status worsened with weight loss, night sweats, evening fever, and decreased visual acuity revealing a severe retinochoroiditis in the right eye. A combined 18-fluorodeoxyglucose positron emission tomography–CT (PET/CT) scan showed significant glucose uptake by mediastinal and peripheral enlarged lymphadenopathies (Figure 1C). An inguinal lymph node biopsy found an epithelioid reactive lymphadenitis without microorganisms or neoplastic cell but was positive for *Toxoplasma* DNA. The treatment was switched to pyrimethamine (50 mg/d) and clindamycin (900 mg/d) for 6 weeks. Since then, the patient has partially recovered his eyesight and is doing well.

Pulmonary toxoplasmosis is a rare condition in immunocompetent subjects (5) and is often life threatening (4). The genotyping analysis of *T. gondii* DNA with 15 microsatellite markers (6) revealed an atypical genotype. Although some allelic combinations were common to those observed in certain South American strains, this genotype was unknown in the database of the French National Reference Center for toxoplasmosis. The isolation of atypical strains is rare in Europe and likely suggests contamination by non-European strains either during residence abroad or after consumption of imported meat (2). The epidemiological investigation of our case revealed that consumption of raw horsemeat imported from Argentina was the most likely source of *T. gondii* infection. Three similar French cases have been published in 2011 (2). In all of these cases, horsemeat was imported from countries in South America (Brazil) and North America (Canada), where atypical strains of *T. gondii* are more common than in Europe.

Factors that might explain the severity of toxoplasmosis with atypical strains in immunocompetent people seem to be complex and more probably associated with lack of adaptive host response than with strain-specific differences in virulence. Unfortunately, animal models that properly mimic human toxoplasmosis are not available, and the determinants of strain-specific differences in virulence for human infection remain unknown. The *ROP18*, *ROP5*, *ROP16*, and *GRA15* loci of *T. gondii* have been associated with virulence in mice. However, because the murine and human immune responses to *T. gondii* are so different, it cannot be assumed that these four virulence loci in mice similarly affect survival in human cells (7). An outbreak in Suriname showed that the same atypical strain could lead to a broad spectrum of clinical manifestations ranging from mild illness to life-threatening disease requiring hospitalization (8). These data strongly suggest that the size of inoculation related to different dietary practices, for example, the degree of doneness for cooked meat, plays a major role in explaining the severity of symptoms in toxoplasmosis.

The PET/CT scan results and the presence of *Toxoplasma* DNA in lymph nodes nearly 2 months after the onset of symptoms highlight the fact that therapy with spiramycin was not effective. Although spiramycin has been used in 3 of 16 French Guiana patients with severe toxoplasmosis and showed a longer delay for apyrexia than pyrimethamine-sulfadiazine (9), there are no supportive data for treating severe toxoplasmosis in immunocompetent patients with spiramycin. In fact, the first-line specific therapy should have been the combination pyrimethamine-sulfadiazine or pyrimethamine-clindamycin, as reported in the literature when symptoms are persistent or severe (10, 11). No relationship has been found between drug susceptibility and *T. gondii* genotype (12).

In conclusion, physicians should keep in mind that severe toxoplasmosis may exist in patients who are immunocompetent, especially when eating undercooked horsemeat by acquiring imported atypical strains that are poorly adapted to humans. We should treat them as soon as possible with a pyrimethamine-sulfadiazine combination—and not only in cases of persistent or severe symptoms. This case and others advocate for an urgent risk assessment of human severe toxoplasmosis from horses slaughtered for food.

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Life-Saving Closure of a Pulmonary Cavity by Endobronchial Valve Placement

*To the Editor*:

Endobronchial valves (EBVs) have been used in management of prolonged air leak from pneumothorax (1–3). Relatively few reports describe such treatment as a life-saving intervention (4, 5). Valves have also been used to cause atelectasis in selected lobes for lung volume reduction in emphysema (6). We describe a case of a massive bronchopleural fistula (BPF) due to a large cavitating pneumonia where EBV placement gave the combined benefits of cessation of air leak and closure of the cavity, resulting in an excellent outcome.

A 29-year-old woman with a 3–pack-year history of cigarette smoking presented with a 3-day history of breathlessness, cough, and fever. She had a history of anorexia nervosa and chronically low body mass index. The patient appeared unwell with mild delirium, respiratory rate 24 breaths/minute, pulse 124 beats/minute, blood pressure 130/74, and temperature 35.9°C. Oxygen saturation was 93% in room air. On examination there were signs of a right lower zone pleural effusion. Chest radiograph (CXR) demonstrated bilateral airspace consolidation especially in the right upper zone together with a moderate-sized right pleural effusion. Emergent pleural ultrasound and placement of a 16-Fr intercostal catheter (ICC) resulted in the drainage of 1.5 L of purulent fluid. Intravenous fluids and antibiotics (ticarcillin/clavulanic acid and metronidazole) were commenced; however, clinical deterioration resulted in transfer to the ICU on Day 2, where the patient was intubated and ventilated. Pleural fluid cultures were positive for *Streptococcus pyogenes* (heavy growth, penicillin sensitive) and *Staphylococcus aureus* (scant growth, flucloxacillin sensitive). On ICU Day 5 a large BPF developed, as signaled by a massive ICC air leak. CXR showed a large right pneumothorax, as well as subcutaneous emphysema. A second 24-Fr ICC was inserted. Chest computed tomography (CT) revealed a large cavity resulting from bronchopneumonia (Figure 1A). Gas exchange parameters worsened: with a set tidal volume of 480 ml, only 250 ml was returned due to the air leak. At this point $Pa_{CO_2}$ climbed from 50 to 60 mm Hg. Pressure support ventilation with PEEP was instituted. In addition acute hypotension led to the diagnosis of a pericardial effusion by echocardiogram requiring percutaneous drainage of 360 ml of purulent fluid. Surgical consultation was obtained, and in view of the patient's extremely poor general condition and the extent of the upper lobe necrosis, lobectomy was not advised. A decision was therefore made to use EBVs. At bronchoscopy through the 8-mm endotracheal tube a balloon catheter (CRE 12-mm balloon; Boston Scientific, Natick, MA) was inflated in the right upper lobe (RUL), demonstrating immediate cessation of air leak. After sizing of airway diameters, three EBVs were placed, two of 4.5 mm and one of 5 mm diameter (Zephyr; Emphasis Medical, Redwood City, CA). Placement took approximately 10 minutes, after which no air leak was observed and all ventilatory parameters immediately improved. Post-procedure CXR showed a residual pleural space resulting from complete RUL atelectasis. Repeat CT chest showed complete closure of the large RUL cavity (Figure 1B). The ICC was removed after 10 days and broad-spectrum antibiotics were continued for an additional 6 weeks. Discharge occurred after 6 weeks in hospital including general rehabilitation. Eight weeks after discharge the patient coughed out one of the valves without adverse sequelae, and 6 months after discharge the remaining two valves were removed at elective bronchoscopy. CXR at that time showed an absence of any cavity in the RUL, near complete resolution of pleural changes, and complete filling of the upper zone pleural space by compensatory expansion of the middle and lower lobes (Figure 1C).

In BPF cases associated with empyema, standard surgical options are complex and include suture closure with muscle pedicle, open pleural drainage and serial debridements, or even pulmonary resection or thoracoplasty (7). EBV in our case dealt with both the cavity and the air leak simultaneously as a first-line procedure. Schweigert and colleagues reported two cases of empyema with a pulmonary cavity. Patients first underwent video-assisted thoracic surgery to manage the cavity, after which EBVs were required for persistent air leak (5). Toma and colleagues also reported two cases of persistent air leak after repeated surgical debridement of lung abscess after pneumonia, both of which ultimately responded to EBV as a second line procedure (8). A key reason for the success of the EBV in our patient was atelectasis of the entire upper lobe. This closed the cavity and stopped the BPF, and decreased the chances of potential adverse sequelae such as hemorrhage or secondary infection. In patients with emphysema balloon testing and CT fissure examination are used to exclude collateral ventilation before EBV; however, in our young patient, the absence of collateral ventilation ensured the success of EBV in closing the cavity (6, 9). Complete atelectasis of the RUL would normally be followed by compensatory expansion of the middle and lower lobe. This did not occur due to the concomitant empyema with lower zone pleural tethering. Because of the residual space there was concern that a low-grade BPF persisted; however, the absence of air leak in the ICC suggested this was not the case, and in time with gradual expansion of the middle and lower lobe and parts of the upper lobe this space was filled. The ability to remove the valves without any adverse effect was rewarding given the size of the initial cavity and the benefit of removing a foreign body from the patient's bronchial tree. A range of other endobronchial treatments exist for control of BPFs; however, EBV has grown in acceptance as