Short Report: Hemophagocytic Syndrome as Uncommon Presentation of Disseminated Toxoplasmosis in an Immunocompetent Adult from Chinese Kunming

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Abstract. Hemophagocytic syndrome is a rare disease that is often fatal, despite treatment. An immunocompetent patient was presented with fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia, which conformed to a hemophagocytic syndrome diagnosis. Despite broad antibiotic treatment, the patient's clinical condition rapidly deteriorated and he died within 8 days of admission. Blood cultures and a serology test were negative; however, based on morphological characteristics, tissue cysts *Toxoplasma gondii* were found in the bone marrow. Based on polymerase chain reaction analysis, identity of the parasite was confirmed. Although very rare, *T. gondii*-associated hemophagocytic syndrome should be suspected in the case of cytopenia or multiorgan failure symptoms. To our knowledge, this is the first fatal toxoplasmosis case reported from China.

INTRODUCTION

Toxoplasma gondii is an important zoonotic infection worldwide and may lead to uveitis, pneumonia, pericarditis, and neurologic disorders in immunocompetent hosts.¹ Hemophagocytic syndrome is a rare, but potentially fatal, disease resulting from unregulated activation and proliferation of lymphocytes.² Hemophagocytic syndrome associated with *T. gondii* infection occurs most commonly in acquired immunodeficiency syndrome (AIDS) patients or transplant recipients,^{3–6} but are very rare in immunocompetent humans. Here, we describe the first case of fatal disseminated toxoplasmosis in a previously healthy adult from China with clinical manifestation conforming to hemophagocytic syndrome.

CASE DESCRIPTION

The patient was a previously healthy 41-year-old male forest policeman, which required him to have contact with wild animals in a virgin forest. His family members indicated that the patient on occasion hunted mammals (hares, civets, etc.) and drank stream water while on duty.

He was admitted to an emergency unit with a 4-day history of fever, adynamia, dry cough, and mental dysfunction. On physical examination, the patient exhibited a temperature of 39.0°C, heart rate of 80, blood pressure of 95/66 mm of Hg, and respiratory rate of 20. Blood chemistry revealed a hemoglobin of 6.2 g/dL (normal: 11–16), red blood cell count of 2,120,000/ μ L (normal: 3,500,000–5,500,000), white blood cell: 2,290/ μ L, with 42.8% neutrophils (normal white blood cell: 4,000–9,000; neutrophils 50–70%), platelets 9,000/ μ L (normal: 100,000–300,000), glucose 9.5 mmol/L (normal: 3.2–5.6), direct bilirubin 23.7 μ mol/L (normal: 1.7–7.1), alanine aminotransferase 104 IU/L (normal: 4–40), aspartate aminotransferase 216 IU/L (normal: 8–40), lactic dehydrogenase 1,528 IU/L (normal: 114–240), triglyceride 3.21 mmol/L (normal: 0.37–1.80), ferritin 23,800 μ g/L (normal: 20–280), fibrinogen 95 mg/dL (normal: 200–400). A blood culture was negative for bacteria

and viruses. Serological testing for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and antinuclear antibody were negative. A chest x-ray revealed an interstitial and alveolar infiltrate. Hepatosplenomegaly was observed using B-ultrasonography and tomography.

On admission, the patient was given an empirical antimicrobial treatment with cefoperazone plus tazobactam and etimicin. However, fever, dyspnea, and dry cough persisted and his clinical condition rapidly worsened and mechanical ventilation was required by the third day following admission. On the fifth day, bone marrow was biopsied for further diagnosis. The patient finally died of multiorgan failure 8 days after admission. Bone marrow examination revealed a few nuclear cells and a great amount of *T. gondii* cysts and tachyzoites (Figure 1) using Wright's stain. The cyst sizes ($N = 13$) ranged from 10 to 25 μ m.

For further assessment of the pathogen, a bone marrow smear was submitted to the parasite research laboratory of Yunnan University. Total DNA from the bone marrow sample was isolated and polymerase chain reaction (PCR) analysis was performed using the *T. gondii*-specific primer pairs TOX4 (CGCTGCAGGGAGGAAGACGAAAGTTG) and TOX5 (CGCTGCAGACACAGTGCATCTGGATT).⁷ The target fragment of 527 bp could be amplified from this sample (Figure 2). The sequence of the PCR product was identical with the published sequence of *T. gondii* (AF146527).

DISCUSSION

Seroprevalence of *T. gondii* infection is common in humans, ~12.3% in China,⁸ but severe, or even fatal cases, are rarely described. Disseminated toxoplasmosis is associated with fever and multivisceral involvement. The organs most often involved are the lungs, heart, and brain, but any organ or system can eventually be involved.^{9–12} In this case, our patient developed an atypical pneumonia, with cavities and pleural effusion. Biological findings revealed elevated concentrations of liver enzymes, glucose, and direct bilirubin, suggesting the patient had developed hepatitis. Although hepatitis B virus and hepatitis C virus are frequent causes of hepatitis, the serology results were negative.

At admission, the patient's laboratory findings included high fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia,

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FIGURE 1. A group of *Toxoplasma gondii* tachyzoites (arrow) in bone marrow smear of the patient, Wright's stain.

hypofibrinogenemia, and hyperferritinemia. These signs and symptoms conformed to the diagnostic guidelines for hemophagocytic syndrome proposed by the Histiocyte Society in 1991¹³ and updated in 2004.¹⁴ Hemophagocytic syndrome has been associated with a variety of viral, bacterial, fungal, and parasitic infections. Infections associated with hemophagocytic syndrome are most frequently caused by viruses, particularly Epstein-Barr virus.² *Toxoplasma gondii* can cause hemophagocytic syndrome that mostly occurs in immunocompromised patients or in transplant recipients; a rare clinical presentation of toxoplasma-associated hemophagocytic syndrome has been reported in an immunocompetent 12-year-old boy in France.¹⁵ Hemophagocytic syndrome is probably underdiagnosed, as *T. gondii*-associated multiorgan failure is usually explained by other more common causes such as sepsis syndrome/shock.^{16,17}

Diagnosis of *T. gondii* in this case was based on the presence of cysts and tachyzoites in a bone marrow smear and molecular characterization. Visualization of tachyzoites or cysts in bone marrow smear is difficult because of their small size. The use of both morphology and PCR supported the diagnosis. The 529 bp DNA fragment have been proved valuable and currently represent a sensitive PCR target for *T. gondii* detection.¹⁸

Congenital infection, ingestion of infected tissues, and ingestion of oocysts are the three main modes of transmission of *T. gondii*.¹⁹ It is likely that the major routes of transmission

are different in human populations with differences in culture, eating habits, and/or environmental factors.²⁰ In this case, the patient resided in Anning Prefecture, Yunnan Province, located in the southwest of China. People living in this area are accustomed to drinking stream water and enjoy eating raw or half-raw meat or animal internal organs as part of their culture. Because the deceased patient regularly performed his duties in a subtropical forest region and was frequently exposed to risk factors, it is difficult for us to determine the incubation period.

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FIGURE 2. Species-specific polymerase chain reaction (PCR) amplification of the 529 bp DNA fragment using the *Toxoplasma gondii*-specific primer pairs TOX4/TOX5. Lanes: 2 kb DNA ladder (M); negative control using TE buffer (A); positive control using *T. gondii* oocysts stored at parasitic research laboratory of Yunnan University (B); and bone marrow of the patient (C).

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