CASE REPORT

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Toxoplasma gondii infection in children after allogeneic hematopoietic stem cell transplantation: A case report and literature review

Lijuan Luo[1] | Nan Shen[1] | Wenjuan Chen[1] | Chengjuan Luo[2] | Xiaohang Huang[2] | Yuelian Jiang[3] | Qing Cao[1]

[1]Department of Infectious Diseases, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[2]Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[3]Department of Pharmacy, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Correspondence
Qing Cao, Department of Infectious Diseases, Shanghai Children's Medical Center, Shanghai 200127, China
Email: caoqing@scmc.com.cn

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ABSTRACT

Introduction: Toxoplasmosis is a life-threatening complication after hematopoietic stem cell transplantation (HSCT). However, for several reasons, clinicians know little about *Toxoplasma* infection.

Case presentation: We report a case of toxoplasmosis that was diagnosed by bone marrow smear and metagenomic next-generation sequencing (mNGS) after HSCT in a boy. Additionally, we summarize the characteristics of toxoplasmosis after pediatric HSCT reported in the literature published in PubMed.

Conclusion: Clinicians should increase their awareness of toxoplasmosis in children after HSCT and implement pre-transplant screening and post-transplant monitoring and prevention in future according to the national conditions of our country.

KEYWORDS
Toxoplasmosis, Hematopoietic stem cell transplantation, Pediatric

INTRODUCTION

Toxoplasmosis is a zoonotic parasitic disease caused by *Toxoplasma gondii* and can be transmitted vertically through the placenta, through consuming contaminated water, food, and uncooked meat, and through other means. *Toxoplasma* infection is prevalent worldwide, with approximately 30% of the world population infected with this parasite.[1] China has conducted two large-scale surveys on human *Toxoplasma* infection, and the infection rate increased from 5.16% in 1983 to 7.88% in 2001.[2,3] With the change in dietary structure, eating habits and increase in pet-keeping, the infection rate of *Toxoplasma* has further increased. The latest survey showed that the current positive rate of *Toxoplasma* antibodies in the general population in China is 8.20%; in 2017, the incidence was 9.69%, and in 2010 it was 7.49%.[4]

T. gondii is an opportunistic, pathogenic protozoan. Eighty percent of people with normal immune function infected with *T. gondii* show no symptoms. *Toxoplasma*-related encephalopathy, ophthalmopathy, liver disease, myocardial pericarditis, pneumonia, skin lesions and even disseminated toxoplasmosis may occur after infection

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in immunocompromised populations.[5] It has been reported that the incidence of *Toxoplasma* infection after hematopoietic stem cell transplantation (HSCT) is 6%–16%,[6] and the mortality rate of *Toxoplasma* infection after HSCT is as high as 60%–90%.[7,8]

Here we described the case of a pediatric patient with *Toxoplasma* infection after allogeneic-HSCT (allo-HSCT) at our hospital and reviewed the relevant literature. We hope to improve clinicians' understanding of *Toxoplasma* infection after pediatric HSCT.

CASE REPORT

A 10-year-old boy was diagnosed with "acute myeloid leukemia M7 type" at our hospital in October 2018, and allo-HSCT was performed at our hospital in March 2019. The donor was the father of the boy (HLA 6/10 loci matched, A, B, DR, DQ loci mismatched). Busulfan (BU)-cyclophosphamide (CTX)-antithymocyte globulin (ATG) was used as the conditioning regimen. Cyclosporine, methotrexate and mycophenolate mofetil were used for graft-versus-host disease (GVHD) prophylaxis after transplantation. Twenty-two days after HSCT, the child began to develop fever without any other symptoms. On examination, apart from a temperature of 39.6°C and small bleeding spots on the skin, we found no abnormalities. Laboratory investigations showed a decreased white blood cell count of 2.8 (normal 4.0–15.0) × 10^9/L , absolute neutrophil count of 1.18 (normal 1.4–6.5) × 10^9/L, platelet count of 18 (normal 100–550) × 10^9/L, and ascendant 1,3-β-D-glucan level of 503 pg/mL (normal < 60). Other results of laboratory tests were negative (e.g. routine urine and stool analysis, blood culture, cerebrospinal fluid culture and general examination, respiratory virus RNA detection, including respiratory virus, adenovirus, influenza, parainfluenza, nasal virus, quantitative CMV, EBV and HBV DNA analysis, HSV and HCV antibody analysis, HIV and syphilis screening, GM test, and T-SPOT). In addition, no positive results were found by abdominal and pelvic ultrasound, chest and abdomen CT, heart color ultrasound, or brain CT. Empirical antimicrobial therapy was given with meropenem, vancomycin, and voriconazole, but the patient's fever was not relieved. Thirty days after HSCT, bone marrow cytological examination and bone marrow culture were performed. Notably, quick-stained bone marrow smears showed tachyzoites suggestive of *T. gondii* (Figure 1). *T. gondii* was further detected with the flow cytometry fluorescence luminescence method in blood samples. Unfortunately, the patient was positive for *T. gondii*-IgG, but negative for *T. gondii*-IgM. The patient underwent brain MRI and fundus examination, and no infectious lesions were found. To confirm the pathogenic infection of this patient, metagenomic next-generation sequencing (mNGS) of the pathogenic agents was employed, and 142 sequence readings of *T. gondii* were detected in the bone marrow. The patient did not keep pets at home, had no history of animal contact, and denied eating raw meat, fish and other habits. After the patient's diagnosis was confirmed as toxoplasmosis, we tested anti-*T. gondii* antibodies in donor, and both IgM and IgG tests were negative. Then, the patient was treated with trimethoprim/sulfamethoxazole (TMP/SMZ) (10/50 mg/kg) + clindamycin (30 mg/kg). After 4 days of treatment, the patient's body temperature returned to normal. After 6 weeks of treatment, the patient was discharged and continued to take TMP-SMZ (4/20 mg/kg per day, 3 times per week) for 6 months. During the follow-up period, there were no signs of toxoplasmosis recurrence. Unfortunately, six months after HSCT, the patient's leukemia relapsed and did not respond well to treatment. The patient discontinued treatment and died 9 months after HSCT.

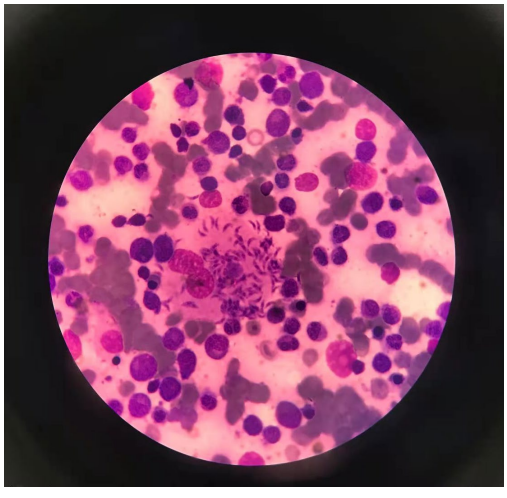

FIGURE 1 Bone marrow smear of the patient after hematopoietic stem cell transplantation (Giemsa-Wright's, 10×). The half-moon-shaped tachyzoites with one pointed side and one blunt side in the center of the image was *T. gondii*.

DISCUSSION

We used "*Toxoplasma gondii* or Toxoplasmosis or *Toxoplasma* infection and children or pediatrics and hematopoietic stem cell transplantation" as the search term and retrieved the relevant literature from PubMed and summarized it, including 12 articles with 26 patients.[8-19] European patients represented 46.2% (12/26) of the patients overall. Detailed information was provided in the literature for 18 patients aged 4–18 years. The underlying diseases included 4 cases of myelodysplastic syndromes, 4 cases of acute lymphocytic leukemia, 3 cases of acute myeloid leukemia, 2 cases of non-Hodgkin's lymphoma, 1 case of chronic myelogenous leukemia, 1 case of liver cancer, 1 case of neuroblastoma, 1 case of Fanconi anemia, and 1 case of immune-mediated encephalopathy. Seventeen patients underwent allo-HSCT, and one patient underwent auto-HSCT. The main characteristics of the patients are summarized in Table 1.

TABLE 1 Clinical characteristics of 26 children with *T. gondii* infection after HSCT

Case characteristics	Number of patients
Region	26
Europe	12
South America	8
North America	5
Asia	1
Sex	18
Male	12
Female	5
Unknown	1
Transplant type	18
Allo-HSCT	17
Auto-HSCT	1
Affected organs	18
Central nervous system	15
Systemic dissemination	4
Retina	4
Skin	1
Symptoms	18
Headache, vomiting, epilepsy, hemiplegia, hallucination, coma linguistic difficulties	15
Fever	8
Visual impairment	4
Rash	2
Respiratory distress	1
Imaging abnormalities	15
CNS MRI/CT	14
Chest CT	1
Recipient Anti-Toxo-IgG before HSCT	10
Positive	8
Negative	2
Recipient Anti-Toxo-IgM after HSCT	8
Positive	2
Negative	6
Autopsy/Biopsy	7
Brain tissue	4
Skin	1
Unknown	2
PCR	13
Cerebrospinal fluid	10
Peripheral blood	6
Bone marrow	1
Bronchoalveolar lavage fluid	1
Vitreous	1
Unknown	1
Outcome	18
Alive	9
Death[†]	9
Treated	4/13
Untreated	2/2

[†]Fifteen patients provided information about their treatment; 2 patients were not treated, and 13 patients received treatment. Four of the 13 patients who received treatment died, both patients who did not receive treatment died. Allo-HSCT, allogeneic hematopoietic stem cell transplantation; Auto-HSCT, autologous hematopoietic stem cell transplantation; CNS, central nervous system; MRI, magnetic resonance imaging; CT, computed tomography; PCR, polymerase chain reaction.

Toxoplasmosis after HSCT mainly manifests as disseminated toxoplasmosis, toxoplasmosis encephalopathy, toxoplasmosis ophthalmopathy and isolated fever.[20] According to our summary of patient data, central nervous system involvement is the most common presentation, accounting for 83.3% (15/18) of the cases. Cranial MRI of patients with central nervous system involvement mostly shows nodules with ring enhancement and can be used for preliminary screening and as a basis for empirical therapy.[6,21] Fever and visual impairment were the other two main manifestations, occurring in 44.4% (8/18) and 22.22% (4/18) of patients, respectively. Therefore, if patients have nervous system involvement symptoms, fever of unknown origin and visual impairment after HSCT, clinicians should consider the possibility of *Toxoplasma* infection.

Toxoplasmosis after HSCT has a high mortality rate, and a significant proportion of patients are not diagnosed until after death. Nine of the 18 patients with complete information that we summarized died of *Toxoplasma* infection, with a mortality rate of 50%. Of the 15 patients whose treatment information were provided, 4 of the 13 patients who received treatment died (30.8%) and both of patients who did not receive treatment died (2/2, 100%). Failure to diagnose and treat is an important reason for the high mortality rate. It was shown that if correctly diagnosed and treated in a timely manner, approximately 48% of *Toxoplasma*-infected patients can completely recover, and the condition of another 13% can be significantly improved.[22] Histopathology, serum immunology and molecular biological methods are the three methods for toxoplasmosis diagnosis. Histopathology is used to confirm diagnoses, but low sensitivity and the need for more invasive procedures limit its clinical application. The serum immunological method has been widely used in clinical applications due to its rapid and sensitive characteristics, but strong immunosuppressive therapy after HSCT affects the production of antibodies. Among the cases summarized in our study, 8 patients underwent *Toxoplasma* antibody detection after transplantation, and IgM antibodies were positive in only 2 patients. Toxoplasmosis after HSCT is usually the result of the reactivation of a latent infection in serum-positive patients; thus, serological tests are mainly used to evaluate the serological status of donors and recipients before transplantation to screen high-risk patients.[5,6] At present, great breakthroughs have been made in the diagnosis and prevention of toxoplasmosis using molecular biological methods. The diagnosis of 13 of the patients we summarized was made by PCR. In this study, *Toxoplasma* infection was finally confirmed by mNGS of the bone marrow fluid. Some scholars have even proposed including PCR detection of *Toxoplasma* in the diagnostic strategy of unexplained fever in patients after HSCT.[23,24] However, the lack of a standardized PCR assay is the main confounding factor and this method needs to be further

studied and standardized.

Considering the high rate of *Toxoplasma* infection in foreign countries, more attention has been given to the evaluation and monitoring of *Toxoplasma* infection after HSCT in those countries. Many researchers have proposed prevention strategies for toxoplasmosis. First, pre-transplantation screening for *Toxoplasma* antibodies can be performed in donors and recipients to identify high-risk patients and allow for preventive measures for seropositive high-risk patients.[5,6,18] In France and 11 other European countries included in the Euro transplant network, serological screening before transplantation is mandatory.[5] Second, PCR can be used to monitor high-risk patients regularly to identify cases of *Toxoplasma* infection as early as possible.[8,23,25] Finally, TMP/SMZ can be used for preventive treatment after HSCT.[6,26] However, at present, routine monitoring of *T. gondii* infection pre- and post-HSCT has not been implemented in China.

There is no consensus on the treatment for *T. gondii* after HSCT. The recommended treatment is divided into two stages: induction therapy and chronic suppressive therapy (secondary prophylaxis). In the induction stage, the first-line recommended regimen is the synergistic combination of pyrimethamine with sulfadiazine plus folinic acid or TMP/SMZ. The induction phase last at least 6 weeks. At the end of induction therapy, secondary prophylaxis should be carried out with smaller doses of pyrimethamine with sulfadiazine plus folinic acid to prevent the recurrence of the disease. The total treatment course is at least 6 months in length.[5,21,26] There is no standard for the termination of treatment after HSCT, but some studies have shown that the $CD4^+$ lymphocyte count may be valuable for guiding the treatment of *T. gondii* infection in HSCT recipients.[14]

Reviewing the diagnostic process of the patient in this case reveals the limitations of our work. *Toxoplasma* antibodies were not screened in the patient pre-transplantation. If we had not found tachyzoites in the bone marrow smear, the diagnosis of the patient may have been either further delayed or missed. If national guidelines are implemented for the screening of patients pre- and post-HSCT and if doctors increase vigilance regarding *Toxoplasma* infection after HSCT, the diagnosis of this infection may become faster and more economical. With the increasing infection rate of *T. gondii* in the domestic population, the infection rate of patients after HSCT is likely to increase accordingly. Therefore, we must improve our understanding and formulate further prevention strategies for incorporation into the national guidelines for our country in future work.

We report this case to suggest that clinicians improve the understanding of *T. gondii* infection after pediatric HSCT, consider pretransplant screening and posttransplant monitoring and prevention, implement timely diagnosis and treatment, and improve the prognosis of this disease.

CONSENT FOR PUBLICATION

Consent was obtained from the patient's guardians.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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