Late-Onset Cerebral Toxoplasmosis After Allogeneic Hematopoietic Stem Cell Transplantation

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Patient:	**Male, 44**
Final Diagnosis:	**Cerebral toxoplasmosis after HSCT**
Symptoms:	**Hemiparesis • muscle weakness**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Hematology**

Objective: Unusual clinical course

Background: Toxoplasmosis is an uncommon but potentially fatal complication following allogeneic hematopoietic stem cell transplantation (HCT). Post-transplant toxoplasmosis is often a reactivation of prior infection and typically occurs within the first 6 months of transplant. Herein, we report that cerebral toxoplasmosis may occur 22 months after allogeneic hematopoietic stem cell transplantation.

Case Report: We describe a case of cerebral toxoplasmosis that occurred 22 months after an allogeneic HCT while the patient was on aerosolized pentamidine for *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis. The disease was only diagnosed after brain biopsy because of atypical MRI appearance of the cerebral lesion and negative *Toxoplasma gondii* IgG antibody test result in the cerebrospinal fluid (CSF). The patient received pyrimethamine and sulfadiazine treatment, with dramatic improvement after several months. The patient is alive 2 years after infection diagnosis, with no evidence of disease and is off *Toxoplasma prophylaxis*.

Conclusions: Cerebral toxoplasmosis can occur late after allogeneic HCT while patients are on immunosuppression therapy, with atypical features on imaging studies and negative *Toxoplasma gondii* IgG antibody test result in the CSF. Pre-transplant serologic screening for *T. gondii* antibodies in allogeneic transplant candidates is warranted. Brain biopsy can be a helpful diagnostic tool for cerebral lesions.

MeSH Keywords: Brain Biopsy • Case Reports • Hematopoietic Stem Cell Transplantation • Late Reactivation • Prophylaxis • *Toxoplasma Gondii* • Toxoplasmosis • Toxoplasmosis, Cerebral

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Background

Toxoplasmosis is an uncommon but frequently life-threatening complication of allogeneic hematopoietic stem cell transplantation (allo-HCT), and is caused by the protozoan parasite *Toxoplasma gondii* (*T. gondii*) [1]. It is the most common central nervous system (CNS) opportunistic infection, with a mortality rate over 50% [2]. Toxoplasmosis is acquired primarily through ingestion of *T. gondii* cysts from undercooked meat or oocysts from fecally-contaminated foods [3]. In allo-HCT patients, toxoplasmosis usually results from reactivation of a latent infection, instead of a primary infection [4,5]. The seroprevalence of *T. gondii* in the United States is approximately 10%, and it is estimated that at least 800 allo-HCT patients are at risk for reactivation annually [6]. Post-transplant toxoplasmosis is more common in endemic countries [4]. Incidence in reported in the literature varies from 0.4% to 9% [7–10]. For example, in the USA, it was found to be 0.3%, while in France it was 5% [4,10]. Toxoplasmosis usually (90%) develops within the first 6 months after HCT, with the highest incidence in the second and third months [5,6,10–13]. Although central nervous system (CNS) infection is not common after HCT, cerebral toxoplasmosis accounts for most post-transplant CNS infections [1,2]. In the literature, we have found only 3 cases (published in 1995, 1998, and 1999) in which toxoplasmosis occurred within the first year of transplant [5,12,13]. The most recent case, reported by Zver et al., discussed a case of late reactivation of cerebral toxoplasmosis that occurred 11 months after allo-HCT in a patient with chronic myeloid leukemia (CML). This case of toxoplasmosis was thought to be triggered by a course of corticosteroid administrated for chronic graft-versus-host disease (GVHD) [5]. Herein, we report a case of cerebral toxoplasmosis that occurred 22 months after allogeneic HCT, which posed a diagnostic dilemma.

Case Report

The patient was a 44-year-old white male diagnosed with precursor B cell Philadelphia-positive acute lymphocytic leukemia (ALL) after developing dysarthria and confusion due to subdural hematoma (with pancytopenia). He received imatinib induction therapy and achieved a complete remission. He then underwent consolidation allo-HCT from his HLA-matched sister after undergoing a fludarabine and myeloablative total body irradiation conditioning regimen. His transplant was complicated by mild cutaneous acute GVHD, and later (at 12 months) by mild oral and musculo-skeletal chronic GVHD. He was treated with sirolimus, tacrolimus, and prednisone. Prednisone was tapered gradually to 5 mg every other day by 22 months post-transplant, while tacrolimus and sirolimus were continued. At that time, he presented with progressive fatigue and shortness of breath, with no fever. Chest X-ray (CXR) showed bilateral pulmonary infiltrates, and he was admitted to the hospital for intravenous antibiotic treatment. Prior to hospitalization, he has been on aerosolized pentamidine (300 mg) monthly for *P. jiroveci* pneumonia (PCP) prophylaxis rather than trimethoprim/sulfamethoxazole (TMP/SMX) due to frequent cytopenia. During hospitalization, he developed confusion and left-sided weakness. He also had worsening thrombocytopenia and anemia, and an elevated LDH with schistocytes on peripheral smear suspicious for drug-induced thrombotic microangiopathy. Tacrolimus and sirolimus were thus withheld. An MRI of the brain showed a non-enhancing T2 hyperintense 1.3 cm circular lesion in the right basal ganglia (Figure 1A). The lesion had a restriction in diffusion-weighted images (DWI) suspicious for infarction (Figure 1B), although it did not follow a typical vascular territory. The neurology team was consulted and MRI spectroscopy showed atypical appearance for possible neoplasm or infarction (Figure 2). Lumbar puncture
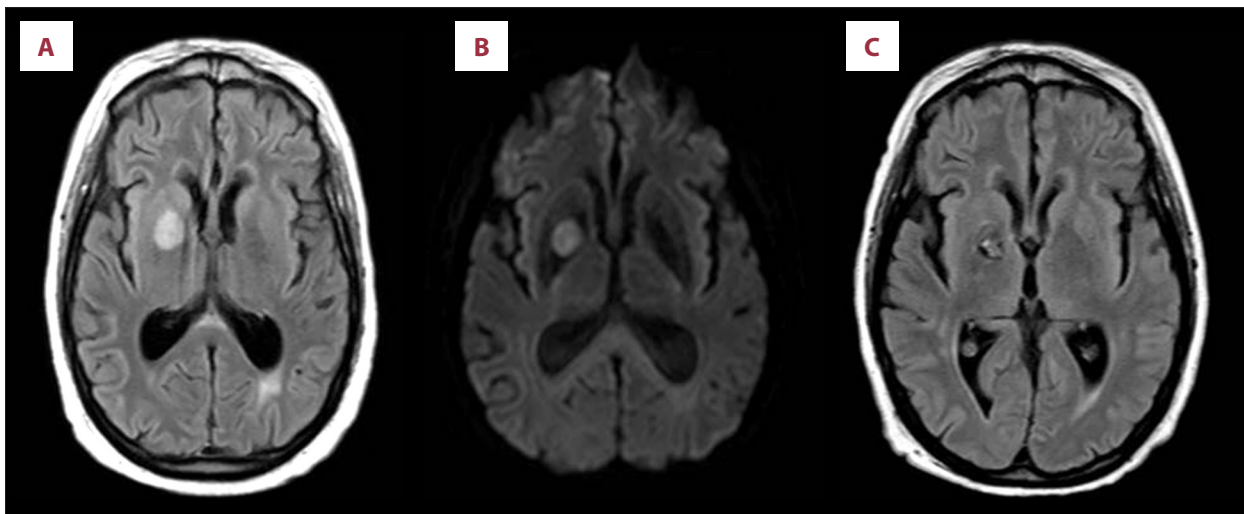

Figure 1. MRI of the brain: (**A**) Hyperintense lesion in the right basal ganglia before treatment (FLAIR). (**B**) Diffusion-weighted image showing a restricted diffusion lesion. (C) Resolved lesion with residual gliosis 9 months after treatment (FLAIR).
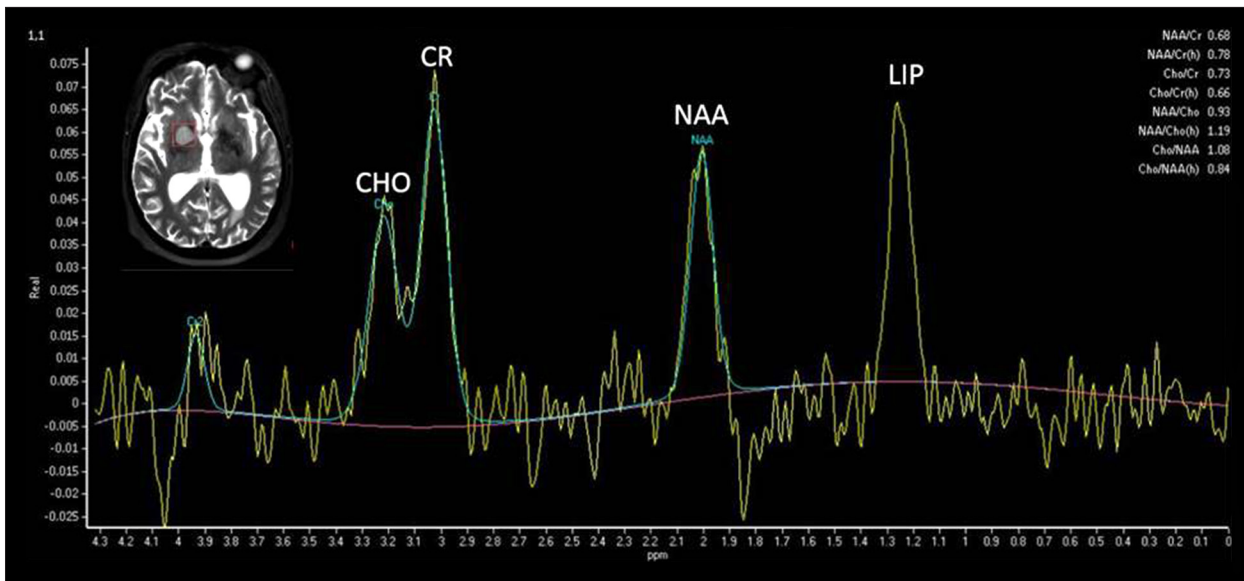
Figure 2. Single-voxel PRESS spectrum acquired within the lesion on a 3T MR scanner at TE=144. Magnetic resonance spectroscopy (MRS) of toxoplasmosis lesions typically demonstrates elevated lactate and lipid peaks. The spectrum in this patient demonstrates no elevation of choline (CHO) to suggest tumor or demyelination. NAA is decreased, (non-specific, and compatible with any neuron-replacing process). At TE=144, lactate peaks (commonly observed with infarcts) typically invert, pointing below the baseline. However, at 3T, lactate may be underestimated at TE=144 due to "anomalous J-modulation". The presence of lactate cannot be confidently ruled in or out by this patient's MRS exam. The tall peak at approximately 1.2 ppm was presumed to reflect a lipid resonance.

was remarkable for a high protein level of 132 mg/dl (normal 14–45), with negative infectious disease workup on the CSF, including polymerase chain reaction (PCR) for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), John Cunningham (JC) virus, cryptococcal antigen test, *T. gondii* IgG antibody test, and bacterial and fungal isolate cultures. Serological tests of viral infections, including CMV, Epstein-Barr virus (EBV), adenovirus, and human herpesvirus 6 (HHV-6)], as well as blood cultures, were negative. His lung infiltration worsened with development of extensive bilateral ground glass opacities and he was intubated and placed on a ventilator. Bronchoalveolar lavage culture grew CMV (transbronchial biopsy was not done) and he received ganciclovir therapy for CMV pneumonia. He was then extubated, but remained with altered mental status and worsening left-sided weakness. A repeat brain MRI (3 weeks following the initial one) showed an enlarging right basal ganglia lesion (1.8 cm) with the same characteristics as in previous imaging, without typical infarct evolution. After neurosurgical consultation, a brain biopsy was considered. His pulmonary infiltration also worsened with increased oxygen requirement and it was deemed appropriate by pulmonary and infectious disease teams to perform a lung biopsy for accurate diagnosis. After extensive discussion of the risks (particularly thrombocytopenia) and potential benefits of the procedure with the patient and his family, the patient underwent an image-guided biopsy of the right basal ganglia lesion, as well as video-assisted
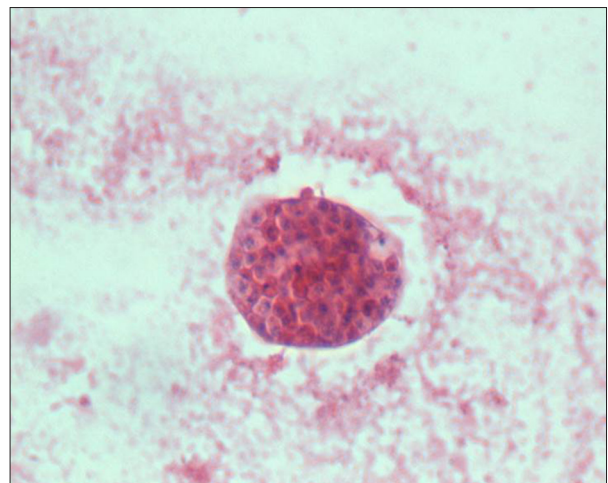

Figure 3. The neuropathic features of toxoplasmosis identified intraoperatively in this smear preparation of the right basal ganglia lesion include numerous bradyzoites within the confines of a sharply-defined, oval-shaped cyst (intraoperative smear preparation viewed through 100× objective).

thoracoscopic lung biopsy, on 2 consecutive days (with platelet transfusion support). The frozen section of the brain biopsy showed necrotic brain tissue with scattered, sharply-delimited, and densely granular oval-shaped structures resembling *T. gondii* bradyzoites (Figure 3). Hematoxylin and eosin staining

demonstrated numerous scattered smaller punctate hema-toxylinophilic structures that were consistent with *T. gondii* tachyzoites within the interstitium of necrotic neutrophils, as well as scattered foamy macrophages indicative of necrosis. Immunohistochemical staining for *T. gondii* was positive, as was the CD68 for macrophages. Other staining for fungal organisms (GMS stain) and acid-fast staining were negative (with appropriate controls). At that time, serum *Toxoplasma* IgG titer was obtained and was elevated at 24.7 international units/ml (negative: <6.5) and IgM was positive. Of note, neither the patient nor his donor were tested for *T. gondii* antibodies before transplant because this was not part of our institutional standard pre-transplant testing at that time. The lung biopsy showed cryptogenic organizing pneumonia (COP) that likely complicated the CMV pneumonia, with no evidence of infectious organisms demonstrated by microbial cultures. He was started on pyrimethamine and sulfadiazine with leucovorin therapy after infectious disease consultation. He was also started on high-dose prednisone 1 mg/kg daily for COP (with gradual taper while he was weaned off oxygen therapy). He was discharged to the rehabilitation unit. The left hemiplegia gradually improved and he was able to go home and walk with assistance. After 9 months of anti-*T. gondii* therapy, a repeat brain MRI showed right basal ganglia gliosis with resolution of the T2 hyperintensity lesion (Figure 1C). The patient was placed on TMP/SMX maintenance for 12 more months. He continues to do well 25 months after the diagnosis of *T. gondii* cerebral infection (he now off TMP/SMX prophylaxis) and 47 months after allo-HCT, with no evidence of disease relapse.

Discussion

T. gondii sero-prevalence in the United States is approximately 10% [6]. While the most common cause of post-transplant toxoplasmosis is reactivation of latent infection, toxoplasmosis can rarely be transmitted from a donor (even if asymptomatic) to recipients [11,14]. Donor-seropositive/recipient-seronegative (D+/R–) patients appear to be at lower risk than donor-seronegative/recipient-seropositive (D–/R+) patients [6]. The current national standards in the United States (Food and Drug Administration, and Foundation for the Accreditation of Cellular Therapy) do not mandate testing of donor or recipient of allo-HCT for *T. gondii* infection. However, published guidelines of the American Society of Blood and Marrow Transplantation recommend testing candidates of allo-HCT for *Toxoplasma* IgG prior to transplant [15]. This testing would obviously be critical for patients from endemic areas. The risk of *Toxoplasma* reactivation is particularly high during the first few months post-transplant, and may occur later in case of delayed immune reconstitution (e.g., with cord blood or haploidentical HCT), or continued immunosuppression for GVHD [6]. A prospective study used weekly blood PCR screening in seropositive

patients undergoing allo-HCT, and detected a 16% risk of reactivation [7] PCR-detected *T. gondii* reactivation in this study preceded clinical presentation by 4 to 16 days. Diagnosis of toxoplasmosis in allo-HCT recipients requires a high index of clinical suspicion because the clinical manifestations of the infection are often suppressed by immunosuppressive therapy [15]. In addition, *T. gondii* antibodies may not be detected in immunocompromised patients [5]. PCR testing is an alternative tool, but in the United States this is restricted to reference laboratories, which often involves delayed turnaround time. Two large reviews of 110 and 386 patients with toxoplasmosis reported that the diagnosis of more than 50% and 27% of the cases, respectively, was made postmortem [4,6]. Cerebral toxoplasmosis should always be suspected in allo-HCT patients with atypical brain lesions. In our patients, the negative *T. gondii* IgG antibody test result in CSF was misleading. Obtaining tissue biopsy may be helpful in certain settings. The criterion standard for diagnosis of cerebral toxoplasmosis is the presence of parasites in pathological specimens. Typically, cerebral toxoplasmosis appears in MRI images as multiple lesions that are hypointense on T1-weighted pre-contrast MRI. On T2-weighted and FLAIR MRI, the lesions are usually hyperintense with focal nodular or ring enhancement after administration of gadolinium contrast [1]. Although ring-enhancing lesions are characteristic of toxoplasmosis, transplant patients may lack this feature, as was the case in our patient, who was on immunosuppressive therapy including prednisone at the time of diagnosis. Steroid therapy can also mitigate febrile manifestation of infection. Although the brain is the primary site of the disease, the lungs, heart, and other organs are rarely involved [11]. The routine use of TMP/SMX for PCP prophylaxis provides protection against reactivation of toxoplasmosis. Several observational studies have demonstrated the efficacy of TMP/SMX in decreasing the incidence of toxoplasmosis following HCT [6,7]. Most of reported cases (around 70%) in allo-HCT occurred in patients who were not on sulfa prophylaxis, whereas only 12% occurred in those on prophylaxis [6]. With the exception of TMP/SMX, medications used for PCP prophylaxis, such as aerosolized pentamidine (like the case in our patient), dapsone, and, atovaquone, have not been shown to be effective for toxoplasmosis prophylaxis following HCT [15]. Aerosolized pentamidine does not penetrate the body site of reactivation, and there are insufficient data regarding the efficacy of dapsone and atovaquone following allo-HCT. Patients seropositive for toxoplasmosis who are intolerant to TMP-SMX should be considered for other prophylaxis regimens, such as clindamycin, pyrimethamine/leucovorin, pyrimethamine/sulfadiazine, or pyrimethamine/sulfadoxine/leucovorin [15]. Since parasitemia may precede clinical *Toxoplasma* infection, regular surveillance of *Toxoplasma* PCR in the blood has been used with a preemptive therapy approach [7].

Conclusions

Cerebral toxoplasmosis may be encountered up to 2 years following allo-HCT, with atypical features on imaging studies and negative CSF antibody testing. Pre-transplant serologic screening for *T. gondii* antibodies in allogeneic transplant candidates is warranted. Brain biopsy continues to be an important and informative diagnostic tool in patients with atypical brain lesions after allogeneic HCT. Blood serological testing may obviate the need for brain biopsy in appropriate settings.

Acknowledgements

Competing interests

Abbreviations

ALL – acute lymphocytic leukemia; **Allo-HCT** – allogeneic hematopoietic stem cell transplantation; **CMV** – cytomegalovirus; **CNS** – central nervous system; **COP** – cryptogenic organizing pneumonia; **CSF** – cerebrospinal fluid; **CXR** – chest X-ray; **D–/R+** – donor-seronegative/recipient-seropositive; **D+/R–** – donor-seropositive/recipient-seronegative; **DWI** – diffusion-weighted images; **EBV** – Epstein-Barr virus; **GVHD** – graft-versus-host disease; **HCT** – hematopoietic stem cell transplantation; **HHV-6** – human herpesvirus 6; **HSV** – herpes simplex virus; **JC** – John Cunningham; **PCP** – *Pneumocystis jiroveci* pneumonia; **PCR** – polymerase chain reaction; **T. gondii** – *Toxoplasma gondii*; **TMP/SMX** – timethoprim/sulfamethoxazole; **VZV** – varicella zoster virus.

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