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Hemichorea–hemiballismus associated with a case of cerebral toxoplasmosis in a hematopoietic stem cell transplant recipient

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Case Report

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Abstract

Due to their immunocompromised state, recipients of hematopoietic stem cell transplants (HSCTs) are at a higher risk of opportunistic infections, such as that of toxoplasmosis. Toxoplasmosis is a rare but mortal infection that can cause severe neurological symptoms, including confusion. In immunosuppressed individuals, such as those with acquired immunodeficiency syndrome (AIDS), toxoplasmosis can cause movement disorders, including hemichorea–hemiballismus. We present the case of a 54-year-old Caucasian male with a history of hypertension and JAK-2-negative primary myelofibrosis who underwent an allogeneic peripheral blood stem cell transplant from a related donor. After the development of acute changes in mental status, left-sided weakness, and left-sided hemichorea–hemiballismus post-transplant, the patient was readmitted to the hospital. Subsequent testing included an magnetic resonance imaging (MRI) of the brain, which revealed multiple ring-enhancing lesions around the thalami and basal ganglia, as well as a cerebrospinal fluid tap that tested positive for toxoplasmosis. The patient was initially treated with intravenous clindamycin and oral pyrimethamine with leucovorin. The completion of treatment improved the patient's mental status but did not improve his hemichorea–hemiballismus. This case illustrates an uncommon complication associated with central nervous system (CNS) toxoplasmosis in stem cell transplant recipients. Due to its rarity, cerebral toxoplasmosis in immunocompromised patients often remains undetected, particularly in HSCT patients who are immunosuppressed to improve engraftment. Neurological and neuropsychiatric symptoms due to toxoplasmosis may be misidentified as psychiatric morbidities, delaying appropriate treatment. Polymerase chain reaction (PCR) assays offer methods that are sensitive and specific to detecting toxoplasmosis and provide opportunities for early intervention.

Introduction

Toxoplasma gondii, henceforth referred to as *T. gondii*, is a rare but opportunistic parasite. Healthy individuals infected with *T. gondii* are typically asymptomatic due to the suppressive efforts of their immune systems. However, immunocompromised patients, such as those undergoing hematopoietic stem cell transplant (HSCT), may develop toxoplasmosis.

Toxoplasmosis most commonly affects the central nervous system, particularly the brain. Infection may manifest as headache, confusion, hemiparesis, convulsions, and other neurological symptoms (Cetinkaya et al. 2022). It may also spread across the body, potentially causing infections such as myocarditis or pneumonitis (Busemann et al. 2012).

We herein describe the case of a 54-year-old male who was found to have been positive for toxoplasmosis following HSCT.

Case report

Mr. X is a 54-year-old married Caucasian gentleman. His past medical history includes gastroesophageal reflux disease (GERD), diverticulosis, and diverticulitis; psychiatrically, he has a history of anxiety, previously treated with escitalopram 10 mg and psychotherapeutic intervention. He reports allergies to sulfa drugs and chlorpromazine. He additionally reports occasional use of alcohol and marijuana in the past.

Mr. X was in his usual state of health until 2005, when routine blood work revealed thrombocythemia, with his platelets measured at 500–600 K/mcL. A physical examination performed on the patient at the time was consistent with a non-palpable spleen; however, a CT of the abdomen

demonstrated a spleen of 13 cm. The patient was then referred to a hematologist for bone marrow tests. He was diagnosed with primary myelofibrosis. Given the stability of his disease, he was treated conservatively and underwent a period of observation followed by periodic laboratory tests until 2011.

In 2011, Mr. X presented to a follow-up with left lower quadrant pain, a significant weight loss of 25 pounds, and fatigue. Bone marrow tested at this time revealed marked hypercellularity, as well as pleomorphic and atypical megakaryocytes with an increase in reticulin fibrosis. Significantly decreased blood counts indicated the necessity of blood transfusions. A positron emission tomography (PET) scan revealed hepatomegaly and splenomegaly, with his spleen having increased in size to 19 × 16.4 cm. Mr. X started taking oral ruxolitinib 20 mg twice daily, with the dosage tapered to 5 mg twice daily as his spleen decreased in size.

The patient continued to report shortness of breath, left upper quadrant pain, and fatigue. He enrolled in a phase 2 clinical trial of a JAK-1 inhibitor, which improved his fatigue. However, given the severity of his symptoms, Mr. X's hematologist referred him to our center regarding therapy with allogeneic stem cell transplantation from his matched brother.

His preparative regimen consisted of busulfan, melphalan, and fludarabine. His pretransplant laboratory workup revealed: blood type O-positive; cytomegalovirus (CMV) and Epstein–Barr virus (EBV) positive; toxoplasmosis, vancomycin-resistant Enterococci, and methicillin-resistant *Staphylococcus aureus* negative. He had no previous fungal history. The donor's pretransplant laboratory workup revealed: blood type A-positive; EBV immunoglobulin (IgG) positive; CMV IgG and toxoplasmosis IgG negative. Given the patient's history of anxiety, he was referred to psychiatry for a pretransplant evaluation. He was started on oral fluoxetine 10 mg daily and oral lorazepam 0.5 mg at bedtime.

In April 2013, Mr. X underwent allogeneic stem cell transplant from an identical human leukocyte antigen sibling donor. His transplant course, however, was complicated by diffuse alveolar hemorrhage on day 17, as well as bilateral retinal hemorrhage, elevated transaminases, CMV viremia, EBV viremia, Klebsiella pneumonia, and *Enterobacter cloacae* bacteremia. Mr. X was readmitted to the hospital in June 2013 for acute mental status changes with unclear etiology, unsteady gait, and hyperkinetic movement of the left upper extremity. His condition eventually progressed to confusion with visual and auditory hallucinations.

An MRI ordered during his hospitalization revealed numerous new hyperdensities within the bilateral basal ganglia, suggesting new, small hemorrhages, numerous enhancing lesions in the right frontal lobe, and lesions in the right superior frontal and middle frontal gyrus. The MRI also noted focal enhancing lesions within the left putamen, a ring-enhancing lesion within the left inferior frontal lobe with surrounding vasogenic edema, and hypoattenuation within the right centrum semiovale. A cerebrospinal fluid (CSF) tap analyzed using PCR revealed positive toxoplasmosis.

The patient then received intravenous clindamycin and oral pyrimethamine with leucovorin. A CSF tap ordered 40 days later returned negative for toxoplasmosis. After some delay due to the patient's documented sulfa allergy, he was started on sulfamethoxazole and trimethoprim. Three months after his initial diagnosis, his clindamycin was discontinued, and he was started on sulfadiazine and leucovorin. At this time, the patient's medication regimen included sulfadiazine 1000 mg twice daily, pyrimethamine 75 mg daily, and leucovorin 10 mg daily. A repeat MRI of the brain performed 6 months later showed slightly decreased diffuse toxoplasmosis.

Psychiatry continued to follow Mr. X during his hospitalization for the management of delirium with olanzapine 2.5 mg in the morning and 5 mg in the evening. His agitation was managed using quetiapine and haloperidol. Upon stabilization of his condition, the patient was first discharged to a rehabilitation center for several days, then home.

Mr. X continued to follow-up with psychiatry as an outpatient. Given his neurological sequelae, he was referred to a clinic specializing in movement disorders in the community. He was started on tetrabenazine 12.5 mg 3 times a day. Following elevated liver function tests, this was decreased to 12.5 mg twice daily. Several months later, the patient began receiving Botox injections in his left scapula and left pectoral muscle every 3 months to decrease hemiballism of the left upper extremity. A follow-up MRI performed 1 year after the initiation of Botox did not show improvements.

Due to reported depressive symptoms including anxiety, poor appetite, insomnia, and low mood, psychiatry started Mr. X on mirtazapine titrated to 45 mg orally at bedtime and lorazepam 0.5 mg twice daily as needed for anxiety. Valium later replaced the lorazepam to manage spasms and anxiety. Mr. X underwent neuropsychological evaluation for assessment of concentration and memory difficulties following his HSCT. Prior to his transplant, the patient presented as a high-functioning individual within a superior range. Following transplant, Mr. X reported difficulties concentrating on multiple conversations, difficulty with multitasking, increased distractibility, and forgetfulness. Formal assessment confirmed these difficulties and found deficits in psychomotor speed and learning and memory, with performance in other domains indicative of relative weakness given estimated premorbid functioning.

Discussion

Before receiving HSCT, patients are required to undergo chemotherapy and/or radiation therapy to prevent transplanted stem cells from attacking their new host. This process renders the individual immunocompromised and more susceptible to diseases and infections (Krüger et al. 2005). While most people infected by *T. gondii* remain asymptomatic throughout their lives, immunocompromised people may suffer from motor deficits, seizures, speech abnormalities, or other neurological symptoms (Martino et al. 2000). They may also develop pneumonitis, myocarditis, or other infections should the toxoplasmosis spread.

PCR testing is one of the most valuable tools for diagnosing toxoplasmosis. Certain PCR techniques can assess a patient's risk for reactivation or primary infection of *T. gondii* (Fricker-Hidalgo et al. 2009; Robert-Gangneux and Belaz 2016). Early identification of the risk would allow providers to prepare for additional preventative or interventional measures during the patient's course of hospitalization.

In addition, HSCT patients who develop toxoplasmosis may experience severe long-term psychological and social consequences. Mr. X suffered significant depression for years after the treatment of his toxoplasmosis, thereby decreasing his quality of life. Loss of function in his arm led to occupational disability. Although it is possible to manage and recover from long-term adverse effects, further research is essential in minimizing these consequences in future HSCT patients who are at risk for toxoplasmosis.

Previous studies suggest that higher levels of depression can negatively affect the recovery process after HSCT (Syrjala et al. 2004). Given the resources to receive psychiatric care prior to

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the procedure, HSCT patients may be able to significantly reduce their depression in the time leading up to the procedure, thereby improving their recovery.

Conclusion

While *T. gondii* infection is often asymptomatic in healthy individuals, in the case of immunocompromised patients, including those undergoing HSCT, it may manifest into toxoplasmosis. The development of toxoplasmosis in HSCT patients can lead to severe neurological symptoms that persist beyond their hospital admission. Such was the case for Mr. X, a 54-year-old male who was found to have toxoplasmosis after receiving HSCT. Mr. X suffered hemichorea–hemiballismus, hallucinations, and altered mental status during his hospitalization. In the years that followed, he continued to have motor and cognitive deficits, which additionally worsened his psychological well-being. Clinicians overseeing the treatment of immunocompromised patients, including those undergoing HSCT, may misattribute the presentation of cerebral toxoplasmosis to psychiatric conditions. This can cause significant delays in treatment, thereby increasing the risk of further morbidity and mortality. Developments in PCR assays may increase the detection of toxoplasmosis and thus provide an opportunity for early intervention.

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