



Case Report

Cerebral toxoplasmosis in a patient with combined variable immunodeficiency

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ABSTRACT

Background: Cerebral toxoplasmosis is an opportunistic infection in patients but has rarely been described in the setting of compromised humoral immunodeficiency. Prompt diagnosis and treatment of the infection is critical in the care of these patients. Medical management is the mainstay of treatment of the infection. There have been very few reports of surgical management of cerebral toxoplasmosis.

Case Description: We describe the case of a 40-year-old male who presented with headache, memory deficits, weight loss, and left-sided weakness in the setting of a known but undiagnosed brain lesion identified 1 month prior. Imaging demonstrated a right basal ganglia lesion which was initially presumed to be malignancy. On further workup including a positive serum test and biopsy including polymerase chain reaction analysis, diagnosis was confirmed as toxoplasmosis. On further investigation, he was found to have deficiencies in immunoglobulins consistent with common variable immunodeficiency (CVID). The patient underwent craniotomy with surgical debulking as repeat imaging showed increased size of mass with new satellite lesions and worsening hydrocephalus.

Conclusion: Cerebral toxoplasmosis is an important differential to consider in cases of intracerebral lesions and should not necessarily be excluded in the absence of compromised cellular immunity. In cases where there is no immunocompromised state and malignancy cannot immediately be established, CVID should be considered as an etiology. Due to the subtlety of CVID diagnosis, careful attention should be paid to history taking and workup for CVID should be considered as soon as possible. Surgical removal of these lesions in conjunction with medications is an effective treatment option.

Keywords: Cerebral toxoplasmosis, Common variable immunodeficiency, Craniotomy, Surgical debulking

INTRODUCTION

Cerebral toxoplasmosis is a life-threatening infection caused by reactivation of the protozoan parasite *Toxoplasma gondii* in primarily immunocompromised individuals.^[27] Toxoplasmosis is typically included in the differential for patients with a history of human immunodeficiency virus (HIV) infection, bone marrow transplant, or other immunosuppressive conditions. Clinical presentation varies widely in regard to the nature of onset and neurological deficit.^[22] A presumptive diagnosis in immunocompromised individuals can be made based on the clinical presentation, observing multiple ring-enhancing lesions on computed tomography (CT)

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or magnetic resonance imaging (MRI), and positive serological testing.^[17] However, the presence of undiagnosed immunodeficiencies and solitary radiographic lesions can lead to delays in toxoplasmosis diagnosis and increasing involvement of neurosurgical specialists.

Common variable immunodeficiency (CVID) is an often underdiagnosed primary immune deficiency characterized by impaired B-cell differentiation, leading to decreased serum levels of immunoglobulin (Ig)G, IgA, and/or IgM.^[26] The presentation of CVID is heterogeneous making it a diagnostic challenge. Most cases present as recurrent sinopulmonary tract infections, though inflammatory and autoimmune manifestations such as autoimmune cytopenia, enteropathy, and chronic lung disease have been reported in more than a fifth of CVID patients.^[18] Toxoplasmosis is prevalent in people with compromised cellular immunity, but it is unusual in people with humoral immune deficiency. There have been a few rare case reports of people with CVID developing cerebral toxoplasmosis^[11,12] and of nonbiopsy neurosurgical management of cerebral toxoplasmosis. Herein, we describe the clinical course and surgical management of a 40-year-old patient with cerebral toxoplasmosis who was later diagnosed with CVID.

CASE REPORT

A 40-year-old Caucasian male with a 2-month history of headache, memory problems, weight loss, chronic diarrhea, and arthralgias, presented to an outside hospital with new-onset significant left-sided weakness impacting his ability to perform his activities of daily living. Medical history was remarkable for recurrent sinus infections and recurrent otitis media. He had no family history of central nervous system diseases or immunologic disease. CT head demonstrated an ill-defined mass in the right gangliocapsular region and midbrain and approximately 10 mm of leftward subfalcine herniation. MRI demonstrated a 4.4 × 2.4 × 4.5 cm right basal ganglia lesion with extension into midbrain, peripheral enhancement with extensive surrounding edema, and 7 mm midline shift [Figure 1]. CT abdomen pelvis revealed

reticulonodular infiltrates of the right and left lower lobes, splenomegaly with mesenteric lymphadenopathy. The patient underwent retroperitoneal CT-guided lymph node biopsy which showed no malignancy. A small bowel push enteroscopy noted acute duodenitis and mild villous blunting. He was seen by an oncologist who suspected his case was consistent with lymphoma or unspecified malignancy and started the patient on steroids. Infectious disease doctor ordered AFB and fungal studies.

He then presented to our hospital with worsening weakness. On examination, he had 0/5 strength on his left upper extremity, left side facial droop, midline palatal elevation, midline tongue protrusion, and right-sided ptosis. Laboratory tests on admission are summarized in Table 1, and they were all within the normal range aside from a leukocytosis to $24.5 \times 10^9/L$. CSF studies showed low glucose, low protein, negative for cryptococcus, and streptococcus. Serum *Toxoplasma* IgM was reactive and IgG was reactive at 17.4. Negative studies included HIV antibody (Ab), rapid plasma regain, *Treponema pallidum* particle agglutination assay, cytomegalovirus IgM, *Rickettsia* Ab, *Brucella* Ab, *Bartonella* Ab, antinuclear antibody, anti-neutrophil cytoplasmic antibody, urine legionella, and pneumococcal antigens. A brain biopsy was performed where four biopsy specimens were obtained at 90° angles and another four biopsy specimens 1 cm deeper were taken in a similar fashion. Pathology was consistent with a histiocyte predominant neuroinflammatory process [Figure 2]. Postoperatively, the patient had no neurological changes.

One week later, despite being on antibiotics and antifungals, his neurological examination deteriorated and he became more obtunded and less responsive. A repeat MRI showed an increase in size of mass with new satellite lesions and hydrocephalus. The decision was made to perform a craniotomy for excision of enlarging mass to debulk and obtain tissue specimens for diagnosis.

During the operation, there was a tough rind that was encountered and dissected around. Initial specimens did not indicate any obvious tumor, and thus, a pericapsular

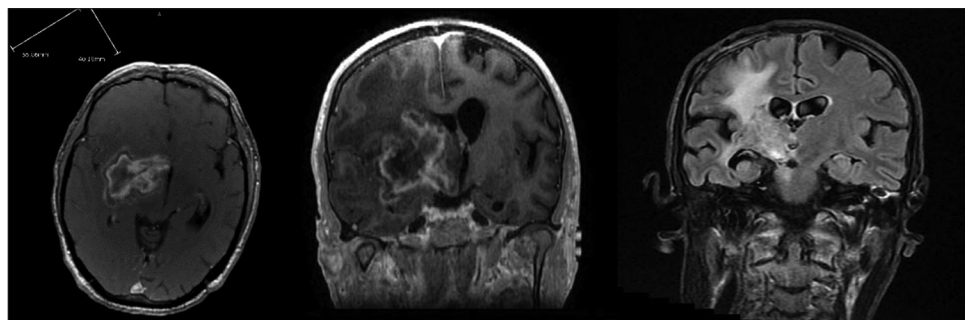


Figure 1: Magnetic resonance imaging brain demonstrating a large, 56 × 40 mm isolated lesion and presence of midline shift.

dissection was continued until most of the mass was removed with a small rind left around the midbrain. Specimen was sent for pathology, culture, and analysis. Postoperatively, he was intubated but opened his eyes to voice and followed commands on his right side. He was extubated on POD 7 and was AO \times 3 with dense left hemiplegia.

Table 1: Laboratory values from admission and cerebrospinal fluid analysis.

Complete blood count	CSF		
WBC (109/L)	21	Color	Colorless
Hb (g/dl)	15.8	Appearance	Clear
Hct (%)	47.8	WBCs	7
Plt (109/L)	170	RBCs	17
		Neutrophils (%)	46
Biochemical findings		Lymphocytes (%)	36
Na (mEq/L)	128	Monocytes (%)	17
K (mEq/L)	4.7	Macrophages (%)	1
Cl (mEq/L)	92	Glucose	56
Ca (mg/dL)	8.7	Total protein	91
Phosphorus (mg/dL)	5.2	VDRL	Nonreactive
Mg (mg/dL)	2.1	Step pneumo	Negative
Glucose (mg/dL)	136	Cryptococcus	Negative
BUN (mg/dL)	17		
S. Cr (mg/dL)	0.55		
Alb (mg/dL)	4.3		
AST (IU/L)	28		
ALT (IU/L)	53		
ALP (IU/L)	151		
T. Bil (mg/dL)	0.4		

Hb: Hemoglobin, WBC: White blood cell, Hct: Hematocrit, Plt: Platelet, Na: Sodium, K: Potassium, Cl: Chloride, Ca: Calcium, Mg: Magnesium, S.Cr: Serum creatinine, Alb: Albumin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, T-Bil: Total bilirubin, CSF: Cerebrospinal fluid, RBC: Red blood cell, VDRL: Venereal disease research laboratory, Strep pneumo: *Streptococcus pneumoniae*

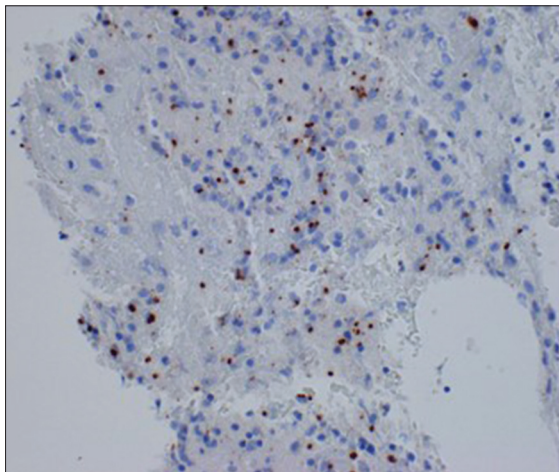


Figure 2: High-magnification image showing a brain biopsy with histiocyte-rich inflammatory infiltrate involving partially necrotic brain parenchyma.

Polymerase chain reaction analysis of the mass was positive for toxoplasmosis gondii [Figure 3]. He was treated with meropenem, pyrimethamine, leucovorin, and atovaquone for 2 months due to a sulfa allergy. One month postoperatively, an MRI brain showed shrinking residual enhancement. He was discharged on hospital day 60. Following the hospitalization, the patient was referred to an allergy and immunology specialist for undetectable Ig levels consistent with severe panhypoglobulinemia with IgG <109, IgA, and IgM <5 mg/dL that was found during his hospitalization. The patient was diagnosed with CVID and was started on IVIG replacement therapy. He continued to improve and was able to mobilize feet in a wheelchair 4 months after surgery and had his suprapubic catheter removed. At 6 months, he was opening his right eye again and started to move his left lower extremity. He also passed his swallow study and had weaned off of tube feeds. Seven months postoperatively, he unexpectedly passed at home from sudden cardiac arrest.

DISCUSSION

Cerebral toxoplasmosis is caused by *T. gondii*, a ubiquitous obligate intracellular parasite.^[7] *T. gondii* is transmitted vertically, zoonotically, through organ transplantation, or by ingesting contaminated food or water. In the United States, it is estimated that *T. gondii* has infected 11% of the population aged 6 and older. One-third of all HIV-infected people demonstrate positive *T. gondii* IgG serology.^[5,13]

Cerebral toxoplasmosis is an opportunistic disease seen in patients with a compromised cellular immunity. Interferon-dependent, CD8+ T cell-mediated immunity is the mainstay of resistance against cerebral toxoplasmosis.^[25] Notably, our patient did not have a deficit of cellular immunity; he was found to have a deficiency of Ig, thus causing a humoral immune deficiency. CVID is a primary immunodeficiency characterized by lack of B-cell differentiation, which causes

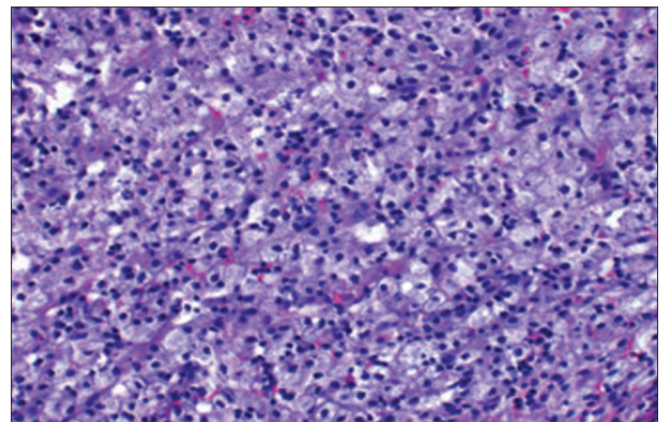


Figure 3: This toxoplasmosis immunostain demonstrates granular nuclear staining consistent with toxoplasma tachyzoite forms without tissue cysts.

defective Ig production resulting in hypogammaglobulinemia. It often becomes clinically apparent in the third or fourth decade of life, as seen in our patient. This defect in humoral immunity typically leads to recurrent bacterial infections. Sometimes, there is a delay in diagnosing these patients as was the case in our patient. He had a history of recurrent ear infections, but he was unfortunately never diagnosed with CVID despite being worked up. There is a lack of literature regarding the prevalence of toxoplasmosis in patients with CVID. There have been a few case reports of cerebral toxoplasmosis in CVID patients reported in the literature. However, none of those patients underwent surgical debulking.^[11,12,21] Interestingly, only one such patient had a defect in humoral immunity without a defect in cellular immunity.^[12] The patient was a 52-year-old female who was diagnosed with toxoplasmosis while being on treatment for CVID. The exact mechanism of toxoplasmosis in patients with humoral immune deficiency is unclear. Experimental data in mice have shown that a reduction of antibody-producing B-cells decreases the resistance against *T. gondii*.^[14] In addition, the treatment of B-cell deficient mice with antibodies reduced mortality and prolonged survival.^[23] It is important for physicians to keep toxoplasmosis in the differential when treating a patient with humoral immunodeficiency who presents with intracerebral mass lesions. In our case, the patient was diagnosed with toxoplasmosis before being diagnosed with CVID. Large-scale studies are required to determine the prevalence of toxoplasmosis in patients with humoral immunodeficiencies to determine if workup for these diseases should be included in all patients with toxoplasmosis.

One rare component of this case was the presentation of cerebral toxoplasmosis as a large solitary lesion, initially thought to be more characteristic of a primary brain malignancy. Given the solitary lesion and presence of enlarged lymph nodes, a presumptive diagnosis of lymphoma was made which contributed to a delay in diagnosis and treatment of the toxoplasmosis. Solitary lesions in an immunocompromised patient are more likely associated with either primary central nervous system (CNS) lymphoma in higher-income countries or tuberculomas in the developing countries.^[6,20] The majority of cases of toxoplasmosis present with multiple small ring-enhancing lesions. Imaging can be used to differentiate toxoplasmosis and CNS lymphoma. However, there is a radiologic overlap between the two. Certain features such as number of lesions (multiple in toxoplasmosis vs. single in lymphoma) and location (basal ganglia in toxoplasmosis vs. brain periphery or corpus callosum for lymphoma) can help differentiate the two.^[9] Perfusion MRI can allow for distinction between the two, with lymphoma lesions showing hypervascularity and increased blood volume.^[10] However, in some cases, it is difficult to differentiate the two radiographically if they do not have the classic features on imaging. Stereotactic biopsy

is warranted for definite diagnosis in those cases. Stereotactic biopsy is an effective procedure with diagnostic success rates as high as 98% with low rates of complications.^[15,29]

Early presumptive diagnosis and empirical treatment are crucial to the management of cerebral toxoplasmosis. However, the absence of an existing immunosuppressive diagnosis as well as atypical radiographic features may delay appropriate treatment including surgery. The previous studies have shown that patients on medical management experience CNS response in 5 days and about 95% of patients show radiographic improvement by day 14 of treatment.^[16,28] Here, we present a case where the patient underwent craniotomy with surgical debulking. Decompressive craniectomies for infectious encephalitis of other etiologies including herpes simplex virus, *Mycoplasma pneumoniae*, and unidentified viral infection have been described in the literature.^[2] Lesional resection of cerebral toxoplasmosis has only been reported a few times in the literature.^[1,3,19] *Toxoplasma* can cause complications like obstructive hydrocephalus due to ventriculitis or compression and blockage of the ventricular system without response to treatment.^[4,8,24] In all of these cases, resection was performed due to worsening clinical status and, in all cases, patients died. At present, no guidelines exist to direct surgical management for cerebral toxoplasmosis. More studies are needed to determine the outcomes of earlier surgical resection in medically refractory patients.

CONCLUSION

We described a patient of cerebral toxoplasmosis with CVID who underwent craniotomy with surgical debulking. In our patient, the patient was initially diagnosed with cerebral toxoplasmosis before being diagnosed with CVID. Although cerebral toxoplasmosis is often associated with HIV, the diagnosis should be included in the differential for any individual with suspected or confirmed immunodeficiency. It should be suspected in patients with humoral immunodeficiency along with cell-mediated immunodeficiency. Furthermore, clinicians should look for undiagnosed immunodeficiency in patients with confirmed diagnosis of cerebral toxoplasmosis. Accurate diagnosis can be challenging especially when in cases, where the immunodeficiency is undiagnosed and radiologic imaging studies demonstrate a solitary lesion as it was seen in our case, which can lead to a delay in treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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