Cerebral Toxoplasmosis: A Case Report with Correlation of Radiographic Imaging, Surgical Pathology, and Autopsy Findings

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ABSTRACT

Cerebral toxoplasmosis is an opportunistic infection of the central nervous system. Certain radiographic findings can be highly suggestive of the disease, but there is considerable overlap with both lymphoma and brain metastases, making the diagnosis difficult or delayed. Herein we present the case of a 77-year-old woman with a history of treated diffuse large B-cell lymphoma who presented with neurological symptoms four months after she was declared to be in remission. Her initial head computed tomography scan showed multiple low-attenuated lesions in her brain and a contrast enhanced magnetic resonance imaging scan showed multiple T1- and T2- enhancing lesions in the basal ganglia and at the gray-white junction. The clinical team was highly suspicious of a recurrence of her lymphoma so she had an extensive workup, including a brain biopsy, which did not lead to a definite diagnosis. After she died, an autopsy was performed, and multiple necrotic lesions were discovered in her brain. Histologic sections demonstrated numerous parasitic organisms, and immunohistochemical staining for *Toxoplasma gondii* was positive, confirming the diagnosis of cerebral toxoplasmosis. This case highlights an unusual case of cerebral toxoplasmosis that was diagnosed at autopsy and reviews the relevant radiographic findings as well as the gross and microscopic pathological features of the disease. *Acad Forensic Pathol.* 2017 7(3): 494-501

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INTRODUCTION

Cerebral toxoplasmosis is a potentially fatal parasitic infection that most commonly occurs in immunocompromised individuals, such as transplant patients and those infected with human immunodeficiency virus (HIV) (1). We present the case of a 77-year-old woman with a recent history of diffuse large B-cell lymphoma (DLBCL), who presented with right sided weakness. Repeated computed tomography (CT) and magnetic resonance imaging (MRI) scans noted multiple lesions throughout both cerebral hemispheres. Numerous clinical tests and diagnostic procedures were performed, including a brain biopsy, but no definitive diagnosis was rendered. The patient died and an autopsy showed multiple cerebral abscesses. Microscopic examination and immunohistochemical studies were diagnostic of *Toxoplasma gondii*.

This case highlights the difficulties of diagnosing cerebral toxoplasmosis. If left untreated, the consequences can be catastrophic; however, accurate clinical diagnosis can be difficult as the imaging findings can overlap with lymphoma and metastatic disease. Surgical biopsies can be nondiagnostic if the abscesses are not able to be sampled safely or thoroughly. This case also emphasizes that cerebral toxoplasmosis should be considered as a possible diagnosis when a patient being treated for, or with recent treatment for, lymphoma presents with a brain lesion, especially multiple lesions, on imaging. Heightened awareness of the occurrence of cerebral toxoplasmosis is needed among practicing autopsy pathologists and medical examiners, as imaging can be nonspecific and surgical biopsies noncontributory.

CASE REPORT

A 77-year-old woman with a recent history of diffuse large B-cell lymphoma (DLBCL), status post six cycles of R-CHOP chemotherapy (which consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) presented with worsening right-sided weakness and repeated episodes of falling. Approximately four months before her presentation, she completed her last cycle of chemotherapy and

had been declared to be in complete remission by her negative positron emission tomography (PET) scan. A noncontrast enhanced CT scan showed multiple low-attenuated lesions in the deep brain nuclei and gray-white junction of the cortical ribbon (**Image 1**, left). A lumbar puncture was performed and multiple laboratory tests were run on the sample. No increase in neutrophils or lymphocytes was identified and glucose levels were within the normal range. Polymerase chain reaction (PCR) testing for herpes simplex virus HSV-1 and HSV-2 was negative and no cryptococcal antigen was detected. The only abnormal finding in the cerebrospinal fluid (CSF) was an elevated protein concentration. More importantly, PCR testing for *Toxoplasma gondii* was not performed on this initial sample. Repeated MRI scans of the head were notable for multiple T1- and T2- enhancing lesions throughout both cerebral hemispheres, concerning for recurrent lymphoma or multifocal metastatic disease (**Image 1**, right). A stereotactic brain biopsy was performed next, as her clinical status was continuing to worsen. Although multiple enhancing lesions were identified on MRI, these were largely located in the basal ganglia and motor/premotor areas, which precluded a safe biopsy of these lesions. The neurosurgical team selected a smaller right frontal lesion to minimize risk. The biopsy demonstrated astrogliosis and a T-cell lymphocytic infiltrate consistent with encephalitis/vasculitis (**Image 2**). A Grocott methenamine silver (GMS) stain was negative for fungi and an acid-fast bacilli (AFB) stain was negative for mycobacteria. Immunohistochemical stains for cytomegalovirus (CMV), HSV, varicella zoster (VZV), SV40 virus, and *Toxoplasma gondii* were performed and were all negative.

Her neurological status continued to decline and she died. Her entire hospital stay was 18 days. Two days before she died, another CSF sample was obtained and a PCR test was performed for *Toxoplasma gondii*. The test was positive, but the results were not complete until a week after her death. Her death certificate was signed by one of the treating physicians as “large cell lymphoma.” The family requested and consented for an autopsy, as they did not understand her rapid decline, especially since she was declared to be in remission with her lymphoma four months

before. At autopsy, her brain demonstrated swelling of the parahippocampal gyri. Multiple necrotic lesions were identified. The largest lesion measured 3 x 3 x 3 cm, was located in the left putamen and globus pallidus and involved the left internal capsule (**Image 3**). There was an additional large lesion in the left basal ganglia and another large lesion in the left parasagittal region, each measuring 3 x 3 x 2 cm. The head of the right caudate also demonstrated softening and this was adjacent to a 2 x 2 x 1 cm area of hemorrhage in the right frontal lobe, which was where the brain biopsy was performed. Innumerable smaller lesions were scattered throughout the cerebral hemispheres. No lesions were identified in the brainstem or cerebellum. Microscopic examination was performed and showed multiple necrotic abscesses with cores of debris and neutrophils. On the periphery of the necrotic cores were numerous neutrophils and mononuclear cells as

well as numerous small capillaries and thrombosed vessels. Outside of these zones of marked inflammation were numerous cellular profiles containing small granules concerning for parasitic cysts along with marked astrogliosis (**Image 4**). Immunohistochemical staining for *Toxoplasma gondii* demonstrated numerous cysts containing bradyzoites and innumerable small, scattered, free tachyzoites (**Image 5**). The heart also demonstrated patchy, acute myocarditis with rare toxoplasma cysts. No lymphadenopathy was noted at autopsy; however, numerous lymph nodes were sampled because of her clinical history of DLBCL. No residual lymphoma was identified. The only other significant anatomic findings were moderate coronary artery atherosclerosis and patchy bronchopneumonia in the lower lobe of the left lung. The clinical team was informed and the death certificate was amended to “cerebral toxoplasmosis.”

Image 1: Noncontrast enhanced computed tomography (left image) demonstrating a low attenuated lesion in the left basal ganglia. Post contrast T1-weighted magnetic resonance imaging (right image) demonstrates a target lesion with an enhancing nodule adjacent to the hyperintense rim.

DISCUSSION

Toxoplasmosis is an opportunistic protozoan infection that most commonly affects patients who have immune deficiencies. The seroprevalence in the United States is reported to be between 20% to 70%, but this varies on geographic region (2). It can be acquired by orally ingesting tissue cysts containing the latent bradyzoite forms of the organism, which occurs most commonly after the consumption of undercooked pork or lamb (3). It can also be acquired by ingesting oocytes that contain sporozoites, which are the product of a sexual cycle that occurs specifically in cat intestines (3). After ingestion, the cysts or oocytes invade host tissues

and differentiate into free tachyzoites. The tachyzoites are what initiate the host immune response and cause the clinical manifestations of the disease. After they are exposed to increased stress from the host's immune response, the tachyzoites can transform into bradyzoites which, as previously mentioned, are the latent encysted forms and can persist indefinitely within the host with a predilection for brain, eye, and muscle tissues (3).

Most primary infections in immunocompetent individuals are subclinical and after the acute infection subsides the encysted organisms remain dormant in the tissues until a decline in immunity occurs. Reactivation

Image 2: This surgical biopsy image demonstrates a mononuclear infiltrate with astrogliosis. The arrows demonstrate representative reactive astrocytes (H&E, x400).

is most commonly seen in patients with HIV, especially when the CD4+ T-cell count falls below 100 cells/ μ L, and it is the most common opportunistic central nervous system (CNS) infection in this population (4).

Acute infection in the brain, which typically follows reactivation of latent bradyzoite-containing cysts, usually manifests as necrotizing abscess formation in the basal ganglia, thalamic nuclei, and the gray-white matter junctions. Necrotizing abscesses are usually characterized by three zones. The central zone consists of coagulative necrosis with few organisms. The intermediate zone is hypervascular and contains nu-

merous neutrophils and mononuclear cells mixed with tachyzoites and cysts as well as numerous reactive astrocytes and microglia. Other findings in this zone include fibrinoid necrosis and perivascular hemorrhage (5). The peripheral zone is composed primarily of astrogliosis and encysted bradyzoites (6). As the necrotizing lesions begin to organize, increased fibrous encapsulation may become evident. It is important to note that the pathological findings depend on the degree of immune impairment with less inflammation and fibrosis seen in severely immunocompromised patients. Chronic lesions consist of cystic spaces containing macrophages and only very rare tachyzoites (5).

Image 3: This image from the autopsy shows a large necrotic lesion in the left putamen and globus pallidus (arrow) with extension into the internal capsule. Additional necrotic lesions are seen at the gray-white junction in the right hemisphere.

Radiographic imaging is extremely useful in the diagnosis of cerebral toxoplasmosis. On noncontrast enhanced CT imaging, the abscesses appear as non or low attenuated lesions (6). On contrast enhanced MRI, a target sign may be seen. On postcontrast T1-weighted imaging, this target sign may appear as a hypo/isointense center with a hyperintense rim. On T2-weighted and fluid attenuated inverted recovery (FLAIR) images, three alternating zones can be seen: a hyperintense core surrounded by an intermediate hypointense region and a peripheral hyperintense rim, delineated by surrounding edema (4, 6). These T2-weighted and FLAIR imaging zones correlate directly to the three distinct components that characterize the necrotizing lesions of an acute infection. The central necrotic zone

correlates to the T2/FLAIR-hyperintense core. The intermediate zone with numerous inflammatory cells, vascular congestion and proliferation, and numerous tachyzoites correlates to the T2/FLAIR-hypointense region. The outer zone, characterized by scanty inflammation, fibrosis, and fewer tachyzoites correlates to the T2/FLAIR-hyperintense rim (4). The reverse is true for the T1-weighted images with the necrotic core correlating to the hypointense T1-zone and the inflammation and vessel rich intermediate zone correlating to the T1-hyperintense rim.

The main differential diagnosis with regards to imaging is CNS lymphoma. Usually, the distribution of lesions can help discriminate between the two. Lym-

Image 4: This section from the necrotic left basal ganglia lesion shows numerous neutrophils and round cellular profiles consistent with parasitic cysts (arrow) (H&E, x600).

phoma lesions tend to be solitary and in a more periventricular or subependymal location while toxoplasma lesions tend to be multiple and located in the basal ganglia, thalamus, and gray-white junction. As previously mentioned, on T1-weighted MRI imaging toxoplasma lesions may show peripheral hyperintensity, which is less commonly seen in lymphoma. An eccentric (asymmetric) target sign may be seen on contrast T1-weighted images, which exhibits a small enhancing nodule along the wall of the enhancing ring. This is highly specific for cerebral toxoplasmosis, but is seen in less than 30% of cases (6, 7). Additionally, lesions in lymphoma tend to be more locally infiltrative and a butterfly-pattern of spread and enhancement is more suggestive of lymphoma.

phoma. However, in reality, there is substantial overlap between imaging and clinical findings, which usually requires a therapeutic trial of antitoxoplasmosis medications to make a diagnosis (4).

Metastatic disease also enters the differential when multiple enhancing lesions are seen on MRI. As with lymphoma, the distribution of the lesions can help discriminate between cerebral toxoplasmosis. Metastases to the brain travel a hematogenous route and the cerebral blood vessels often branch acutely and have reduced diameters at the corticomedullary junctions (8). Thus, the interface of cortex and white matter is a preferential site for the vast majority of metastases

Image 5: This histologic section of the left basal ganglia lesion demonstrates positive brown immunohistochemical staining for *Toxoplasma gondii* (x600). The arrow shows a cyst containing bradyzoites. The arrow head demonstrates a representative free tachyzoite.

as compared to the deep brain nuclei lesions of toxoplasmosis.

In addition to HIV-infected patients, cerebral toxoplasmosis also occurs in other immunosuppressed individuals, such as those who have undergone bone marrow transplant (BMT). There are only rare case reports of toxoplasmosis in patients with hematologic malignancies independent of BMT (7). Our patient fell into this category as she completed her sixth and last round of chemotherapy for DLBCL approximately four months before she started developing neurological symptoms. Her chemotherapy regimen was R-CHOP. Rituximab does have a good safety profile; however, concerns of increasing risk of infection are being raised. It does cause a rapid depletion of B-cells, but may also influence T-cell immunity and predispose patients to opportunistic infections (7). This exact mechanism of T-cell immunity impairment is not entirely understood at the present time.

In this case, the clinicians were favoring a diagnosis of cerebral lymphoma. With her history of DLBCL and her relative immunocompetent state, infection was lower on the differential. The classic “target sign” was not appreciated until her last MRI scan, which occurred only a few days before her death. Radiographically, cerebral lymphoma and toxoplasmosis can appear very similar; however, as previously described, there are differences that can help support one over the other.

CONCLUSION

Encephalitis due to *Toxoplasma gondii* occurs worldwide and follows the ingestion of cysts or oocytes. Central nervous system involvement is almost always an opportunistic infection occurring in immunocompromised patients, but in rare instances can be seen in relatively immunocompetent patients. It is a serious disease that, if left untreated, can have devastating consequences, including death.

Contrast weighted MRI findings usually demonstrate multiple enhancing lesions, which overlaps with lymphoma and metastatic disease; however, the distribution of lesions and potential presence of the asym-

metric target sign can help distinguish between these potential pathologies. If most of the cerebral abscesses are in the deep brain nuclei or in eloquent cortex (such as the motor strip or language areas), a biopsy may not be able to be performed or a suboptimal lesion may be sampled and be noncontributory. In our case, the patient’s initial cerebrospinal fluid sample was not tested for *Toxoplasma gondii* and she was not given treatment for toxoplasmosis, which may have led to a different clinical outcome. The diagnosis was finally rendered at autopsy, once again establishing it as the gold standard for pathologic diagnosis.

It is very important for practicing neuropathologists, general autopsy pathologists, and forensic pathologists to be aware of the gross and microscopic findings of cerebral toxoplasmosis, especially during autopsies of immunocompromised patients, in order to render a correct anatomic diagnosis. Additionally, this case emphasizes the importance of consented hospital autopsy cases for quality improvement by uncovering previously undiagnosed major findings that may affect patient outcome or treatment.

REFERENCES

- 1) Abedalthagafi M, Rushing EJ, Garvin D, et al. Asymptomatic diffuse “encephalitic” cerebral toxoplasmosis in a patient with chronic lymphocytic leukemia: Case report and review of the literature. *Int J Clin Exp Pathol*. 2009 Mar 15; 3(1):106-9. PMID: 19918334. PMCID: PMC2776259.
- 2) Lee GT, Antelo F, Mlikotic AA. Best cases from the AFIP: cerebral toxoplasmosis. *Radiographics*. 2009 Jul-Aug; 29(4):1200-5. <https://doi.org/10.1148/rg.294085205>.
- 3) Weiss LM, Dubey JP. Toxoplasmosis: a history of clinical observations. *Int J Parasitol*. 2009 Jul 1; 39(8):895-901. PMID: 19217908. PMCID: PMC2704023. <https://doi.org/10.1016/j.ijpara.2009.02.004>.
- 4) Masamed R, Meleis A, Lee EW, Hathout GM. Cerebral toxoplasmosis: case review and description of a new imaging sign. *Clin Radiol*. 2009 May; 64(5):560-3. PMID: 19348854. <https://doi.org/10.1016/j.crad.2008.09.016>.
- 5) Ellison D, Love S, Chimelli L, et al. Cerebral toxoplasmosis. In: *Neuropathology a reference text of CNS pathology*. 3rd ed. New York: Elsevier; 2013. p. 409-11.
- 6) Abdel Razek AA, Watcharakorn A, Castillo M. Parasitic diseases of the central nervous system. *Neuroimaging Clin N Am*. 2011 Nov; 21(4):815-41, viii. PMID: 22032501. <https://doi.org/10.1016/j.nic.2011.07.005>.
- 7) Savsek L, Opaskar TR. Cerebral toxoplasmosis in a diffuse large B cell lymphoma patient. *Radiol Oncol*. 2016 Feb 16; 50(1):87-93. PMID: 27069454. PMCID: PMC4825343. <https://doi.org/10.1515/raon-2014-0042>.