Cerebral Toxoplasmosis in a Patient on Methotrexate and Infliximab for Rheumatoid Arthritis

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Abstract

Cerebral toxoplasmosis is a rare disease predominantly found in immunocompromised hosts. However, cerebral toxoplasmosis has not been frequently described in association with the use of immunosuppressive medications. We herein report a case of cerebral toxoplasmosis in a 76-year-old Caucasian woman on methotrexate and infliximab for rheumatoid arthritis. The patient presented with right facial droop, slurred speech and difficulty walking. In addition to receiving methotrexate and infliximab and owning a cat, she had no other obvious risk factors. Imaging studies were not conclusive; however, brain biopsy confirmed the diagnosis. Serology was positive for anti-toxoplasma immunoglobulin G. Cerebral toxoplasmosis should be included in the differential diagnosis of patients under immunosuppressive medication who present with neurological manifestations.

Key words: cerebral toxoplasmosis, rheumatoid arthritis, immunosuppressive medications

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Introduction

Toxoplasmosis is usually the result of the reactivation of latent infection by *Toxoplasma gondii* in patients with immune suppression, such as that due to acquired immunodeficiency syndrome (AIDS), organ transplantation, hematopoietic stem cell transplantation, or cancer chemotherapy (1, 2). The difficulty in making the clinical diagnosis of cerebral toxoplasmosis is attributed to the lack of pathognomonic clinical or radiological features (1). In immunocompetent asymptomatic individuals, latent infection has been reported to be associated with psychiatric diseases, such as schizophrenia, inferring its subtle neurological effects (1). We herein describe a patient diagnosed with cerebral toxoplasmosis following treatment with methotrexate and infliximab for rheumatoid arthritis (RA).

Case Report

A 76-year-old Caucasian woman presented to the emergency room with right facial droop, slurred speech and difficulty walking. She had noticed progressively worsening right-sided weakness, slurred speech and right facial droop for one week. Two days prior to presentation, she had been noted to be forgetful and experienced difficulty in finding words. Her past medical history included diabetes mellitus, hypertension, RA, chronic kidney disease and chronic stable thrombocytopenia. While her family history was noncontributory, she had a pet cat of unknown age and duration. She was receiving chronic treatment with high-dose methotrexate (17.5 mg once every week), which had been tapered to 2.5 mg per week. She was also receiving infliximab (Remicade; 7.5 mg/kg every 6-8 weeks), with the last infusion being six weeks before presentation. On a neurological examination, all cranial nerves were intact, with the exception of right central facial palsy. Her motor strength was 5/5 in the left extremities and 4/5 in the right extremities, with normal tone and sensation. She exhibited dysmetria and moderate hyperreflexia on the right side.

A complete blood count revealed thrombocytopenia, with a platelet count of 94,000/µL, white blood cell count of 5,000/µL, hemoglobin level of 11.4 g/dL and mean corpuscular volume of 91 fL. Blood chemistry showed an albumin
level of 2.7 g/dL, creatinine level of 1.06 mg/dL, Interna-
tional Normalized Ratio (INR) of 1.17, glucose level of 145
mg/mL, glycosylated hemoglobin level of 6.7 %, aspartate
aminotransferase (AST) level of 40 IU/L and alanine
aminotransferase (ALT) level of 16 IU/L. Head CT (Fig. 1)
demonstrated extensive vasogenic edema involving the left
cerebrum and an ill-defined area of decreased attenuation
near the posterior aspect of the left putamen. In addition,
there was a mass effect on the left lateral ventricle, with an
approximate 0.4 cm of subfalcine herniation to the right (arrow).

A left thalamic stereotactic brain biopsy was performed
for tissue diagnosis. The pathological examination (squash
preparation) showed extensive necrosis and inflammation
with lymphocytes and plasma cells, consistent with the pres-
ence of an abscess, with an encysted organism (trophozoites)
indicating toxoplasmosis (Fig. 3). The tissue sections
were stained with GMS silver stain and found to be negative
for fungi. HIV antigen and antibody screening was negative.
Toxoplasma immunoglobulin M was negative (<0.55), while
immunoglobulin G was positive (>900 IU/mL). Due to the
patient’s sulfa allergy, she was started on therapy with once
daily pyrimethamine (75 mg), clindamycin (600 mg) and
leucovorin (25 mg). After the procedure, she remained neu-
rologically stable and was discharged to the transitional care
unit.

Discussion

Toxoplasma gondii is a ubiquitous obligate intracellular
protozoan that causes latent infection in 30% of the world’s
population (1). In most infected individuals, the organism
remains dormant, and clinical reactivation is often associated
with host immunosuppression. The usual presentation in im-
munosuppressed patients includes meningoencephalitis, pneu-
momitis and disseminated infection (1). Focal neurological
deficits are also common in immunocompromised pa-
tients (3). In a retrospective review of 85 AIDS patients with
cerebral toxoplasmosis (4), the most frequent clinical mani-
festations were headache (89%), hemiparesis (88%), fever
(54%) and seizures (45%). As expected, patients with corti-

cal lesions were found to be at greater risk of seizures than
those with white matter disease (4). Ten (8.5%) patients did
not present with any focal neurological signs (4). Mean-
while, the oculomotor nerve (66%) was the most frequently
involved cranial nerve among the 14% of patients with cran-
ial nerve deficits (4).

The Centers for Disease Control and Prevention (CDC)
has proposed four criteria for establishing the diagnosis of
cerebral toxoplasmosis, including the proper clinical setting,
consistent findings on imaging, positive serological studies
and a therapeutic response to treatment (5).

Of late, the use of immunosuppressive medications, such as
adalimumab, rituximab, etc., has increased significantly.
A Cochrane database systematic review was carried out in
2011 to compare the rates of serious adverse events, includ-
ing tuberculosis reactivation, in all tumor necrosis factor
(TNF) blocker trials published to date (6). Tuberculosis re-
activation exhibited an odds ratio of 4.68 with a 95 CI of
1.18-18.60 (6). Although toxoplasmosis was not compared
in this review, to the best of our knowledge, only a few
cases of toxoplasmosis associated with immunosuppressive
agents have been reported. Nardone et al. reported the de-
velopment of cerebral toxoplasmosis in a patient on
adalimumab for RA (7). In addition, Lassoued et al., who
documented two cases of toxoplasmic chorioretinitis follow-
ing anti-TNF alpha treatment (with adalimumab, infliximab
and etanercept) for RA, suggested measuring the toxoplasma
antibody titer prior to the initiation of anti-TNF alpha ther-
apy (8). Cerebral toxoplasmosis associated with immunosup-
pression medications have also been reported by Safa G. (9)
and Nakamura T. (10). Young et al. reported a case of cere-
bral toxoplasmosis in a patient receiving multiple immuno-
suppressive medications, including methotrexate, infliximab,
prednisone and leflunomide, for RA (11).

Methotrexate obviously causes immunosuppression; how-
ever, there is only one reported case of toxoplasmosis asso-
ciated with the use of methotrexate in an otherwise im-
munocompetent patient. Horiuchi et al. reported this associa-
tion in a 60-year-old woman with a history of RA who had
been on treatment with methotrexate and prednisolone for 20 years prior to presentation (12). She exhibited multiple brain lesions involving the bilateral globus pallidus, right thalamus and left dentate nucleus of the cerebellum (12). CT images usually reveal either hypodense lesions with ring enhancement or nodular enhancing lesions (13). T2-

Figure 2. MRI of the brain without (2A) and with contrast (2B), as well as a coronal section (2C) and flair image (2D), demonstrated a 2.9-cm irregular lesion (red arrow) centered in the left putamen with thin peripheral enhancement and a number of smaller punctate cortical enhancing lesions involving the brain parenchyma, mostly in cortical locations, suggesting metastases.

Figure 3. Squash preparation slides showed extensive necrosis and inflammation with lymphocytes and plasma cells, consistent with an abscess, and an encysted organism (trophozoites-arrow), indicating toxoplasmosis.
weighted MRI images show multiple basal ganglia lesions with high-intensity signals or the “eccentric target sign,” a small nodule in a ring-enhancing lesion, or the “concentric target sign,” with concentric alternating zones of hypo- and hyper-intensity (13, 14). If the diagnosis is in doubt, a bi-target sign,” with concentric alternating zones of hypo- and hyper-intensity, or the “concentric with high-intensity signals or the “eccentric target sign,” a weighted MRI images show multiple basal ganglia lesions with high-intensity signals or the “eccentric target sign,” a small nodule in a ring-enhancing lesion, or the “concentric target sign,” with concentric alternating zones of hypo- and hyper-intensity (13, 14). If the diagnosis is in doubt, a biopsy is recommended, particularly to rule out other CNS pathologies (15).

The most frequent therapy for cerebral toxoplasmosis is pyrimethamine and sulfadiazine along with folinic acid to reduce hematological complications associated with pyrimethamine (13). Other alternative drugs used for the treatment of cerebral toxoplasmosis include clarithromycin and pyrimethamine, sulfamethoxazole and trimethoprim, and clindamycin and pyrimethamine for patients allergic to sulfonamide drugs (13). The most common duration of therapy is six weeks (13). Cerebral toxoplasmosis was successfully treated with intravenous clindamycin (600 mg thrice daily) for three weeks in a 30-year-old AIDS patient with a history of sulfamethoxazole allergy, with symptomatic improvement noted within two days and resolution of the lesion on repeat head CT at three weeks (16).

Cerebral toxoplasmosis should be considered in the differential diagnosis of patients receiving immunosuppressive medications, such as methotrexate, rituximab, adalimumab and infliximab, who present with neurological manifestations. Although there is no evidence for testing patients for toxoplasmosis prior to treatment or primary prophylaxis if positive, this strategy may be considered on a case-by-case basis weighing the risks and benefits carefully. Knowledge of the patient’s seropositive status aids close monitoring and the ability to provide early treatment, if necessary. Further data are needed regarding the risks and benefits of pretesting and primary prophylaxis for this potentially life-threatening disease.

The authors state that they have no Conflict of Interest (COI).

References