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Case Report

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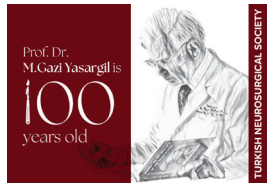

Complex Differential Diagnosis Between Cerebral Toxoplasmosis and Primary CNS Lymphoma in Immunocompromised Patients: The Value of Brain Biopsy

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ABSTRACT

We report the case of a 24-year-old woman who received immunosuppressive treatment for systemic lupus erythematosus. In her past medical history, she had been treated for disseminated toxoplasmosis (ocular and cardiac). Four months later, she was hospitalized and treated for a presentation suggestive of cerebral toxoplasmosis. The diagnosis of primary central nervous system lymphoma (PCNSL) was finally made using stereotactic brain biopsy; however, the evolution was rapidly fatal within 6 days after admission. We discuss the challenge of differential diagnosis between cerebral toxoplasmosis and PCNSL in immunocompromised patients and the role of brain biopsy in patient management.

KEYWORDS: Cerebral toxoplasmosis, Primary CNS lymphoma, Immunosuppression, Brain biopsy, Radiological characteristics

ABBREVIATIONS: CNS : Central nervous system, **PCNSL:** Primary central nervous system lymphoma, **CT:** Computed tomography, **MRI:** Magnetic resonance imagery, **DNA:** Deoxyribonucleic acid, **CSF:** Cerebrospinal fluid, **HIV:** Human immunodeficiency virus, **EBV:** Epstein barr virus, **PCR:** Polymerase chain reaction

INTRODUCTION

Immunocompromised patients are predisposed to numerous opportunistic diseases of the central nervous system (CNS). The clinical and radiological presentations of these pathologies are often polymorphous, and biological tests are limited by problems of sensitivity and specificity. Thus, the borders between these pathologies are often blurred, making therapeutic choices difficult for clinicians. The differential diagnosis between toxoplasmosis and primary central nervous system lymphoma (PCNSL) is particularly problematic, especially in cases with severe clinical presentation (8). In this case report, we discuss the clinical, radiological, and biological features of both diseases and attempt to define appropriate management of these challenging patients. In addition, we discuss the place of brain biopsy in the diagnostic workup.

CASE REPORT

A 24-year-old woman was diagnosed with systemic lupus erythematosus at 18 years of age (mucocutaneous involvement and impure nephrotic syndrome). Immunomodulation with hydroxychloroquine and mycophenolate mofetil was introduced without complications between 2016 and 2021. In August 2021, she was hospitalized for acute myocarditis with heart failure that required extracorporeal membrane oxygenation. The etiological workup was consistent with disseminated toxoplasmosis with cardiac and ocular involvement, prompting the administration of corticosteroid boluses and use of pyrimethamine and clindamycin. Given the suspicion of resistant toxoplasmosis, a relay with high-dose trimethoprim and sulfa-

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methoxazole was performed. The progression was slowly favorable, and she was discharged three months later. Clinically, she presented with sequelae of *Toxoplasma* chorioretinitis and left ventricular dilatation, with a left lateral ventricular ejection fraction of 40%.

Four months later, she was admitted to the emergency department for a clinical presentation associated with confusion, nausea, and fever, which persisted for one week. A brain CT scan revealed multifocal lesions that were spontaneously iso- or hyperdense, with annular contrast and perilesional edema. The patient was transferred to the neurosurgical intensive care unit. On arrival, the patient was apyretic, drowsy, and confused. Brain MRI was performed, which showed multiple lesions, with annular contrast and perilesional edema, with areas of diffusion restriction, some of which were the site of hemorrhagic remodeling (Figure 1). One of these lesions showed the classic "eccentric target sign." Based on the MRI findings, the neuroradiologist suggested cerebral toxoplasmosis. The infectious disease specialist suggested a very likely relapse of cerebral toxoplasmosis on the basis of imaging and clinical history. Lumbar puncture was contraindicated owing to the mass effect. We initiated an exhaustive biological workup and resumed anti-toxoplasmosis treatment with trimethoprim and sulfamethoxazole in this otherwise non-compliant patient. Even if all evidence pointed to cerebral toxoplasmosis, we wanted to eliminate the hypothesis of PCNSL or "dual pathology." A stereotactic biopsy of the largest left frontal lesion was therefore performed 18 hours after admission to support the diagnosis of toxoplasmosis. During surgery, tissue appeared to be necrotic; however, no intraoperative histological analysis was performed owing to the late hour. Corticosteroids were subsequently added to antiparasitic treatment. A post-biopsy CT scan showed no complications.

On day two post-biopsy, the patient was found in a coma (Glasgow score, 5), prompting intubation and administration of hypertonic saline. A CT scan showed overall stability of the lesions and their mass effects. We then decided to implant an intracranial pressure sensor (16 mmHg after optimal sedation). An infectious disease opinion confirmed the hypothesis of cerebral toxoplasmosis and advised an increase in the doses of sulfamethoxazole and trimethoprim due to a probable resistant form of the disease, given the episode of August 2021. On day four, the evolution was marked by refractory intracranial

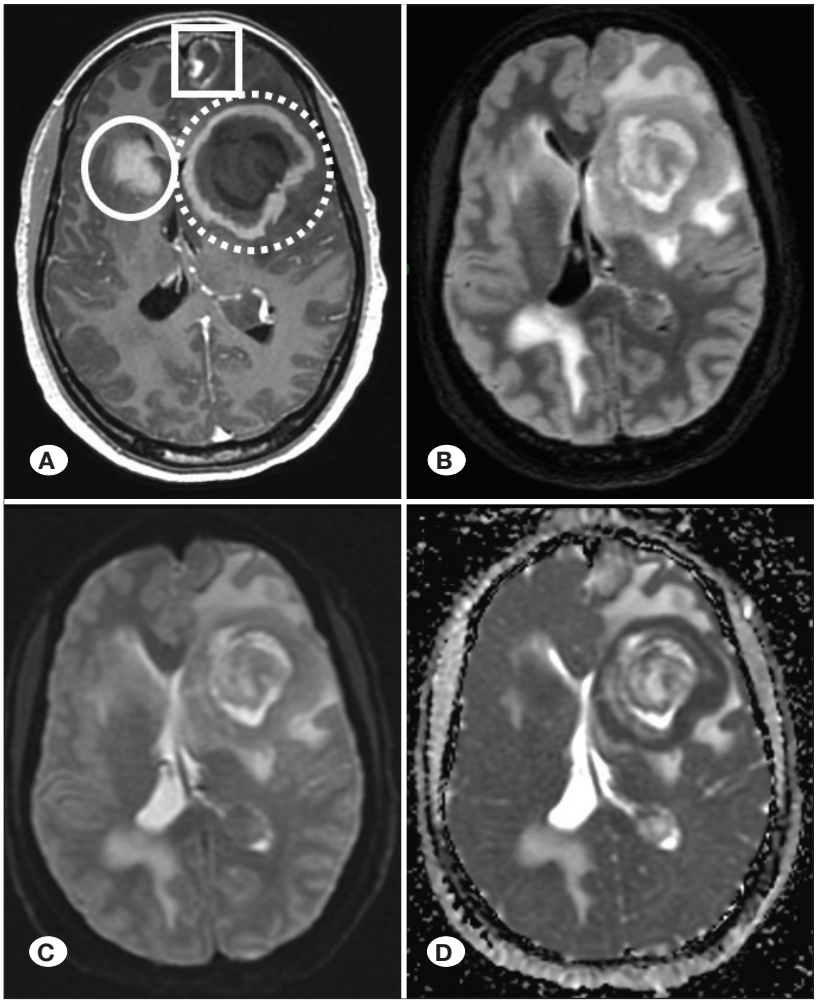

Figure 1: Brain MRI at the admission. T1 after gadolinium injection **(A)** showing lesions with different appearances. The lesion in the square shows an "eccentric target sign." The lesion in the full circle shows homogeneous enhancement. The lesion in the dotted circle shows annular enhancement surrounding the necrotic center. T2 FLAIR **(B)** showing significant perilesional edema, except for the peri-ventricular lesion (full circle) in the injected sequence. DWI **(C)** and ADC **(D)** show heterogeneous signals.

hypertension of up to 60 mmHg despite maximum medical treatment (triple sedation, corticotherapy, hypothermia, and thiopental), which motivated the installation of a right frontal external ventricular shunt. On the same day, we obtained the final histological findings from the brain biopsy, which showed a large B-cell lymphoid proliferation consistent with PCNSL, with a negative *Toxoplasma* test. A neuro-oncological opinion recommended the continuation of high-dose corticosteroid therapy and the introduction of immunotherapy with rituximab. Unfortunately, the short-term evolution was ultimately fatal, with cardiorespiratory arrest requiring five cardioversions. Given the seriousness of the situation, a cerebral MRI was performed, which revealed bilateral ischemic lesions in the region of the posterior cerebral arteries, with signs of brainstem damage. Given the severity of the cerebral lesions and catastrophic prognosis, it was decided in a collegial and multidisciplinary manner, with a consensus on the disproportionate character of chemotherapy—which would have the undesirable effect of aggravating cerebral edema in the context of hyperhydration—not to initiate an escalation of active therapies. The evolution was rapidly negative, and the patient died six days post-biopsy.

Written informed consents were obtained from the individuals (and/or legal representatives) for the publication of the cases.

DISCUSSION

Immunocompromised patients may develop many diseases that affect the CNS. These patients present a diagnostic challenge because their clinical and radiological presentations are extremely polymorphic (Table I) (8).

Cerebral toxoplasmosis corresponds to the endogenous reactivation of dormant cysts of the ubiquitous protozoan *Toxoplasma gondii* due to immune deficiency. It causes a nonspecific neurological presentation with an inconsistent fever (10). Brain imaging reveals rounded lesions, which are multifocal in 69% of cases (6), spontaneously hyperdense, in iso or hypo T1, with variable T2 signal. The lesions show ring enhancement after injection, sometimes with a classic "eccentric target" appearance. The utilization of MR spectroscopy for examination may yield beneficial results in identifying findings consistent with lymphoma. In the absence of serum IgG, infection is unlikely (7), but seroprevalence is high in the general population. Detection of parasitic DNA in the cerebrospinal fluid (CSF) is highly specific but has a lower sensitivity (approximately 50%) (1). The first-line treatment is a combination of pyrimethamine and sulfadiazine, which should be initiated without delay (6).

PCNSL is a rare form of extra-nodal non-Hodgkin's lymphoma, accounting for 3.4% of all CNS tumors (20). It is most often a diffuse large B-cell lymphoma for which the only known risk factor is immunosuppression. The clinical presentation is nonspecific and subacute in onset, with a median time to diagnosis of 35 days (3). The radiological presentation of PCNSL in immunocompromised patients is often misleading (15), with more frequent multiple lesions (30–80% vs. 20–40% in immunocompetent patients) and an absence of contrast reported in 30% of cases. CSF analysis (cytomorphology, flow cytometry, lactate dehydrogenase iso-enzyme, beta2-microglobulin, IL-10, EBV PCR, etc.) is a valuable aid, but only allows the diagnosis of PCNSL in 30% of cases, even in specialized laboratories (14). Finally, brain biopsy is most often necessary for definitive diagnosis, and analysis of the flush fluid of biopsy seems to reduce the delay in diagnosis with excellent sensitivity and specificity (2). Induction chemotherapy is usually based on high-dose methotrexate.

Thus, when toxoplasmosis is suspected in an immunocompromised patient, an unclear presentation (well-conducted prophylaxis, negative serology, radiological appearance)

Table I: Clinical and Radiological Features of Cerebral Toxoplasmosis and PCNSL

	Toxoplasmosis	PCNSL	
		Immunocompetent	Immunocompromised
Clinical features	Nonspecific (intracranial hypertension, seizure, focal neurological deficit…)		
Lesions	Multifocal (69%) Subcortical / Basal ganglias	Single (60-80%) Periventricular	Multifocal (30-80%)
CT-scan	Hypodense	Iso or hyperdense	+/- spontaneous hemorrhage
MRI	T1: iso or hyposignal T2: variable signal Gado: ring enhancement DWI/ADC: variable	T1: iso or hyposignal T2: iso or hypersignal Gado: intense/homogenous enhancement DWI: hypersignal with drop in the ADC Spectroscopy: fall in NAA, increase in choline, peak in lipid and lactates Perfusion: BBB rupture	Gado : enhancement often irregular or annular, and absence of contrast in up to 30% of cases DWI/ADC: variable Spectroscopy/Perfusion: often difficult to interpret

CT: *Computed tomography,* ***MRI:*** *Magnetic resonance imaging,* ***PCNSL:*** *Primary central nervous system lymphoma,* ***Gado:*** *Gadolinium,* ***DWI:*** *Diffusion weighted imaging,* ***ADC:*** *Apparent diffusion coefficient,* ***NAA:*** *N-acetylaspartate,* ***BBB:*** *Blood brain barrier.*

should lead to the suggestion of brain biopsy (11). Similarly, if the test treatment is ineffective or if the clinical presentation is too worrying to risk waiting for an effect, a brain biopsy should be rapidly considered. Immunosuppression was the only factor associated with obtaining a diagnosis of neurological pathologies of unknown etiology from a reported series of brain biopsies (9). The diagnostic yield of brain biopsies in HIV-positive patients is high, exceeding 96% (16,19). Brain biopsy can be performed under stereotactic conditions (using a Leksell frame or robot) (18), or using a neuronavigation system. Regarding the risk of the procedure, in a series of 1500 brain biopsies, one study reported only 3% symptomatic complications (13). The biopsy-related mortality rate was less than 1% in several studies (12,13). Moreover, the risk of complications of a brain biopsy must be weighed against the risk of the natural evolution of an undiagnosed and untreated pathology. Overall, the benefit-risk balance of performing a brain biopsy appears to be favorable in immunocompromised patients.

Finally, it should be noted that the presence of one brain pathology does not exclude the simultaneous presence of another. "Dual pathologies" in immunocompromised patients have been described in many autopsy series of HIV subjects, with a rate varying between 1 and 17% (4,5). For instance, a case series described several cases of HIV patients in whom brain biopsy revealed concomitant PCNSL and cerebral toxoplasmosis (17).

CONCLUSION

This case illustrates the difficulty in differential diagnosis between cerebral toxoplasmosis and PCNSL in immunocompromised patients, with consequences that may involve diagnostic and therapeutic decisions. If a non-invasive workup leaves any doubt, and in particular if the clinical presentation is severe, stereotactic brain biopsy should be rapidly considered. The benefit/risk ratio appears to be very favorable. If intraoperative examination of the biopsy sample is not possible, cytomorphology and flow cytometry of the rinsing fluid seem to be interesting alternatives to reach a rapid and proper diagnosis of PCNSL.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: BM
Data collection: ML, BM
Analysis and interpretation of results: ML, MB
Draft manuscript preparation: ML
Critical revision of the article: BM
All authors (ML, BM) reviewed the results and approved the final version of the manuscript.

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