

# Cerebral Toxoplasmosis in a patient with Pneumocystis: a case report

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**Abstract:** Acquired Immune Deficiency Syndrome, or AIDS, is characterized by a clinical condition in which the body's defenses suffer a gradual depletion, making it susceptible to a wide variety of infections. Among these, neurotoxoplasmosis is a characteristic opportunistic infection caused by *Toxoplasma gondii*. This infection generates numerous neurological deficits that can regress if early diagnosis and intervention are carried out. However, underdiagnosis of these cases due to incorrect management or inaccurate diagnosis leads to damaging and permanent results due to the expansive nature of the mass, which affects a wide range of organic functions. It is then associated with infection by *Pneumocystis jirovecii*, also characteristic of immunodeficient patients, demonstrating a synergism between the mechanisms that facilitate the infectious process. Because of the seriousness of these infections and their association, a clinical picture like this must be well visualized.

**Keywords:** Acquired Immune Deficiency Syndrome; Neurotoxoplasmosis; *Toxoplasma gondii*.

## 1. Introduction

Neurotoxoplasmosis (NTX), known as cerebral toxoplasmosis, is a protozoan, opportunistic infection caused by the parasite *Toxoplasma gondii*. The clinical picture is often associated with immunodeficiency, and it is one of the main opportunistic diseases in patients with Human Immunodeficiency Virus (HIV). It ranks third as the defining infection of Acquired Immunodeficiency Syndrome (AIDS) and is the most common cause of brain abscess in these individuals [1-3]. The cerebral form of toxoplasmosis is a clinical condition that leads to neurological deficits, compromises functionality, can lead to coma and

its outcome is potentially fatal. Early recognition and intervention are crucial to minimizing the morbidity and mortality associated with the disease [4-6]. Diagnosis can be challenging, so the clinical picture and monitoring the progression of the disease should be complemented by imaging tests such as computed tomography (CT), magnetic resonance imaging (MRI) or other radiographic tests, specific serology, histopathology, and cerebrospinal fluid (CSF) tests. The latter has high specificity and low sensitivity [7-9].

Expansive nodular brain lesions resulting from NTX have recurrent radiographic characteristics and manifest as single or multiple, with a mass effect, oval, deep, often surrounded by a marked halo of edema evidenced on contrast, small hemorrhagic foci, signs of intralesional bleeding and associated with significant perilesional edema. Topographically, it has a predilection for the basal ganglia region, the cortico-subcortical region in the deep white matter or in the transition between white and gray matter and can be seen in the posterior fossa [1, 4, 9].

MRI is more sensitive than CT but should only be used if the CT scan is inconclusive. One study showed that MRI can find up to 40% of lesions not found on the CT scan, which would influence patient management. Some MRI images, such as hypodense rings or lesions with nodular enhancement, lesion surrounded by perilesional edema, are highly characteristic of cerebral toxoplasmosis, just as some locations can be suggestive such as basal ganglia and frontal lobe.

Definitive diagnosis is made by stereotactic CT-guided biopsy, but in most cases, this is not necessary. A presumptive diagnosis of neurotoxoplasmosis can be made. The differential diagnosis of focal neurological disease in these patients includes: primary central nervous system (CNS) lymphoma; mycobacterial infection, e.g. tuberculoma; fungal infection, e.g. cryptococcosis; Chagas' disease; bacterial abscess; neurocysticercosis; brain metastases; and, rarely, progressive multifocal leukoencephalopathy (PMLE), which can be distinguished on the basis of imaging studies, as PMLE lesions generally involve white matter rather than gray matter, without the use of contrast and do not produce a mass effect [9,10].

This case highlights the difficulties of diagnosing NTX. If left untreated, the consequences can be catastrophic. However, an accurate clinical diagnosis can be difficult, as imaging findings can overlap with lymphoma and metastatic disease. This case also emphasizes that CT should be considered as a possible diagnosis when a patient undergoing or recently treated for lymphoma presents with a brain lesion, especially multiple lesions, on imaging. Greater awareness of the occurrence of cerebral toxoplasmosis is needed, as imaging can be non-specific and surgical biopsies non-contributory.

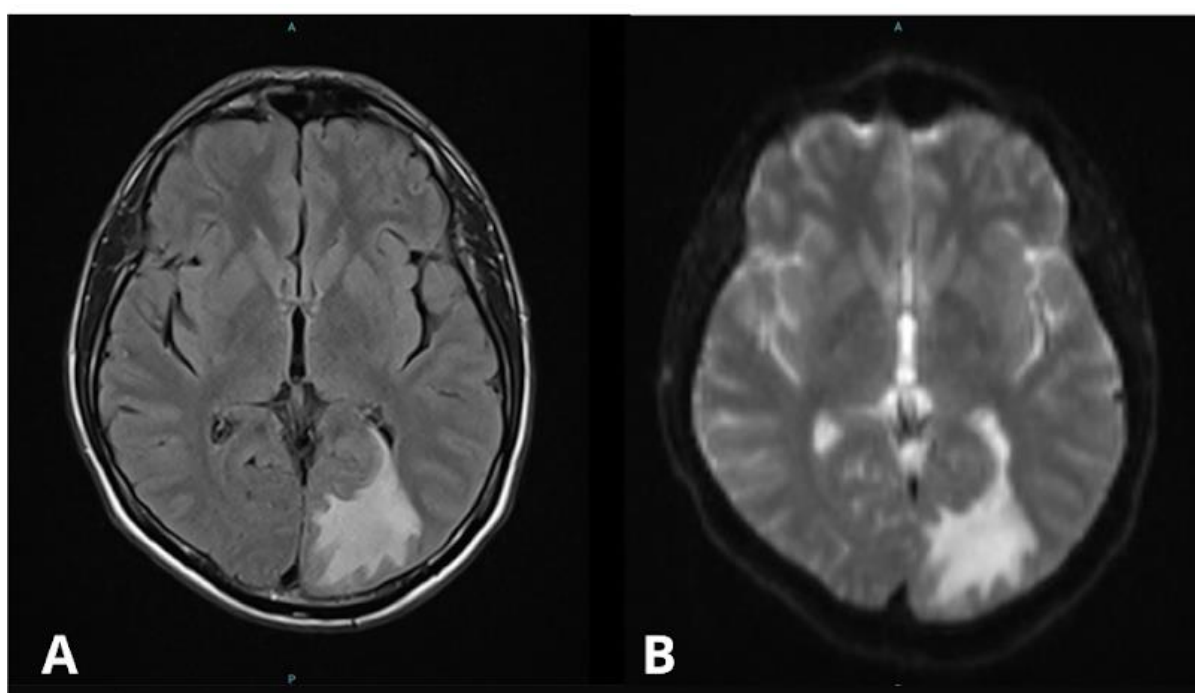
In this sense, ophthalmic involvement in BD is frequent and an important cause of morbidity. One of the most important ocular manifestations is uveitis, whose average age of onset is between 20 and 30 years in male patients and 30 years in female patients [6]. In addition, extraocular manifestations with visual repercussions are also characteristic, such as neuritis, a rare condition characterized by inflammation of the optic nerve, which can lead to symptoms such as loss of vision, blurred vision, ocular pain and altered color perception, which can cause permanent damage [7]. With this information, the treatment of ophthalmic manifestations, such as biotechnological agents, is remarkably effective, improving intraocular inflammation, visual acuity and helping to reduce acute exacerbations. They also help to reduce the use of systemic immunosuppressants, including corticosteroids [8].

Diagnosis is essentially clinical, and inflammatory diseases are characterized by multifaceted episodes of idiopathic origin, without the identification of a specific antigen or antibody that defines the immune response [9]. Complementary tests help in the differential diagnosis and exclusion of potential complications, such as cerebrospinal fluid analysis, magnetic resonance imaging and computerized tomography [10, 11]. However, it is understood that BD is potentially serious, especially when the uvea, central nervous system and great vessels are affected. It is therefore necessary for doctors to be familiar with the forms of BD, its natural evolution, as well as its diagnosis and treatment, to improve

the patient's prognosis. This case report emphasizes the importance of recognizing optic neuritis as a possible presenting symptom of BD, which is a rare clinical feature.

## 2. Case Report

In September 2022, a 40-year-old man with a history of severe headache for two days associated with nausea presented at the doctor's office. Denying associated nausea, he said that physical exercise or daily activities did not make the headaches worse. She also denied photophobia. When asked about her visual acuity, she reported a relative reduction. On physical examination, she was in good general condition, eupneic, ruddy, anicteric, hydrated, and afebrile. She had no alterations in her cardiovascular, respiratory, digestive, or genitourinary systems, nor did she complain of pain in her limbs. Upon fundoscopy, no alterations were observed. Homonymous hemianopsia was also observed. An MRI, cerebrospinal fluid examination and metastasis screening were requested.



**Figure 1:** MRI of the brain of a patient with neurotoxoplasmosis showing a ring enhancing lesion with a thick but smooth rim. Surrounding vasogenic edema and mass effect. Central restricted diffusion. In A, Axial Flair. In B, Axial DWI with restricted diffusion.

## 3. Discussion

### 3.1 *Pneumocystis carinii* and *Toxoplasma gondii* infections

After the central nervous system, the lung is the main site of *T. gondii* infection in HIV-positive patients. Toxoplasmosis should be considered in cases of advanced HIV, with a CD4 count of less than 100 cells/ $\mu$ l and poor adherence to antiretroviral therapy [12]. Pulmonary toxoplasmosis presents as a serious condition with the following clinical manifestations: rales, shortness of breath, cough, fever, myalgias, arthralgias and lymphadenopathies. This clinical picture simulates many other common pulmonary conditions in immunocompromised patients, including pneumocystis pneumonia.

In a study of HIV-infected patients aged between 18 and 65 (mean age  $35.2 \pm 0.3$  years), it was found that in fatal cases, the frequency of pneumocystis pneumonia in the *T. gondii* seropositive cohort was ten times higher than in the seronegative cohort (in which case tuberculosis infection was more common). These data suggest that there may

be synergism between *T. gondii* and *P. jirovecii*. This synergism could explain the increase in cases of co-infection of these two pathogens in HIV-positive patients, and also the increase in diagnoses of pneumocystis pneumonia due to undiagnosed toxoplasmosis pneumonia. Therefore, the recognition and treatment of *T. gondii* in HIV-positive people is important not only to prevent lung lesions due to toxoplasmosis but may also play a role in preventing pneumocystis pneumonia [13].

### 3.2 Toxoplasmosis of the Central Nervous System in the Acquired Immunodeficiency Syndrome

With the advent of the acquired immunodeficiency syndrome (AIDS) epidemic, the first cases of cerebral toxoplasmosis associated with this syndrome were reported in the mid-1980s [17-19]. Currently, this pathology is the main cause of expansive focal lesions in PLWHA [16] and is the most prevalent opportunistic infection in the CNS in patients living with HIV [31,32], representing the most prevalent mass effect lesion in these individuals, especially with an LT-CD4+ count of less than 200 cells/mm [3].

The clinical presentation varies according to the topography of the brain lesions and is usually subacute. The most recurrent clinical manifestations are headache and focal signs (hemiparesis, dysphasia, and other motor alterations). Fever, convulsions and altered mental state may also be present [15]. Neurotoxoplasmosis most often results from a reactivation of latent infection, although a small number of cases can also be acquired acutely, which can develop neurological manifestations of this disease, just as in cases of reactivation of the latent form [14]. By way of illustration, one study showed that 30% of AIDS patients seropositive for *Toxoplasma gondii*, with an LT-CD4+ count of less than 200/ $\mu$ l, developed reactivated cerebral toxoplasmosis [23].

In this context, the most widely accepted thesis regarding the relationship between the two pathologies suggests that immunosuppressed patients have a disturbance in the response of anti-parasitic T cells and are thus unable to fight the parasitic microorganism *Toxoplasma gondii* [20]. It is also possible to postulate that the AIDS virus itself and the dysregulation of microglia and astrocytes may contribute to the reactivation of neurotoxoplasmosis, since individuals with this syndrome harbor a high cerebral viral load due to the replication of the virus in microglia and astrocytes [21,22].

Regarding the occurrence of *T. gondii* infection in PLWHA, there is variation according to geographical location, since studies have shown that the prevalence, morbidity, and mortality related to this co-infection are higher in low- and middle-income countries [24], such as those in Latin America and Africa, among others [24, 25].

About treatment, early access to combined antiretroviral therapy (cART) significantly reduces the incidence of neurotoxoplasmosis in PLWHA [26-28]. In addition, the use of antitoxoplasma therapy can help in the differential diagnostic approach [16, 29, 33]. Behcet's Syndrome is a pathological condition that encompasses a diverse spectrum of clinical manifestations of a polysystemic nature. The disease usually manifests itself in the 30s and 40s, with a predominance of males [12, 13]. However, the above-mentioned patient is in his second decade of life and has no positive laboratory or imaging results for BD but has ocular symptoms such as neuritis and genital ulcers. It should be noted that ocular involvement is a manifestation present in approximately half of all cases of BD, with the possibility of amaurosis occurring in up to 20% of affected patients. The ocular lesions observed in the patient are characterized by being bilateral, non-granulomatous, recurrent, and inflammatory in nature.

The prognosis becomes unfavorable when the posterior segment of the eye is involved, and can manifest itself in conditions such as periphlebitis, diffuse vascular process, retinitis and vitritis [14, 15]. Therefore, the diagnosis of Behcet's Disease is essentially clinical due to the heterogeneity of its presentation. In 1990, the International Study Group for Behcet's Disease (ISGBD) introduced additional diagnostic criteria. However, it is essential to emphasize that these criteria should not be used in isolation to diagnose individual cases.

The disease is usually treated with immunosuppressive drugs and corticosteroids, such as Azathioprine and Cyclosporine A [16], with good results with alpha-interferon [17]. In this case, the treatment prescribed was Azathioprine 50mg, which has the characteristic of controlling inflammation and the symptoms of the disease, such as oral ulcers, specific lesions, and ocular inflammation. However, Azathioprine can promote the generation of reactive oxygen species with mutagenic potential, making it a possible carcinogenic agent [18]. This risk becomes more significant after a period of continuous treatment of approximately 10 years or when the accumulated dose reaches 600 grams or more [18].

Furthermore, the medication Colchicine, with an initial prescription of 0.5mg, has been widely used as a fundamental approach to treating the disease, due to its ability to exert beneficial effects in inhibiting the functions of neutrophils, due to their hyperactivation in BD [19]. Despite showing limitations in cases of more severe manifestations, treatment with colchicine results in a reduction in the incidence of oral and genital ulcers and erythematous lesions, as well as providing relief from the symptoms of arthritis [20, 21].

Colchicine is commonly employed in the treatment of Behçet's disease due to its anti-inflammatory and immunomodulatory properties. This autoimmune disease is characterized by chronic inflammation of small and medium-sized blood vessels, affecting various parts of the body. Colchicine acts by inhibiting microtubule formation, interfering with the processes of chemotaxis and phagocytosis, resulting in reduced leukocyte migration and, consequently, decreased inflammation. Additionally, colchicine demonstrates efficacy in controlling specific symptoms associated with Behçet's disease, such as recurrent oral aphthae, through the suppression of the inflammatory response, which may contribute to improving the quality of life for patients [10, 12, 21, 22]. It is worth noting that BD is one of the main causes of long-term morbidity and mortality in its sufferers, making its recognition and treatment essential for a better outcome [22]. For this reason, it is important to carry out differential diagnosis and scientific disclosure of less frequently reported diseases.

#### 4. Conclusion

In conclusion, the co-occurrence of neurotoxoplasmosis and *Pneumocystis jirovecii* infection in individuals with Acquired Immune Deficiency Syndrome (AIDS) underscores the critical importance of timely and accurate diagnosis. Neurotoxoplasmosis can result in significant neurological deficits, but early intervention can lead to regression of these deficits. However, the expansive nature of the mass in the brain can lead to permanent damage if not properly managed. Moreover, the synergy between these opportunistic infections highlights the complexity of AIDS-related illnesses and the need for a comprehensive approach to patient care. Therefore, it is imperative that healthcare professionals are well-informed and vigilant in recognizing and addressing these infections to improve the prognosis and quality of life for AIDS patients.

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