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AIDS-associated central nervous system lymphoma: the great mime. A case report and literature review

C. Chirico[1], I. Izzo[1], S. Casari[1], C. Cattaneo[2], F. Doglietto[3], F. Castelli[1]

[1]Department of Infectious Diseases and Tropical Medicine, Spedali Civili General Hospital - University of Brescia, Brescia, Italy
[2]Department of Hematology, Spedali Civili General Hospital - University of Brescia, Brescia, Italy
[3]Department of Neurosurgery, Spedali Civili General Hospital - University of Brescia, Brescia, Italy

ABSTRACT: HIV-associated primary central nervous system lymphoma (PCNSL) is an aggressive malignancy that usually occurs in the setting of advanced immunosuppression. Its atypical radiological behavior poses a challenge to the differential diagnosis with opportunistic infections of the CNS.
Here we present a case of PCNSL in the setting of AIDS: after a comprehensive work-up of radiological and laboratory assessments, brain biopsy was necessary to uncover the diagnosis.

Keywords: Primary central nervous system lymphoma, AIDS, Diagnosis.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive subtype of B non-Hodgkin lymphoma. It represents the second cause of intracranial mass lesion in HIV-infected patients[1], with a prevalence of 12.3% among the AIDS-population in the USA. It usually affects severely immunosuppressed patients, with a median CD4+ count at diagnosis of 14 cells/uL, and carries a poor prognosis, with an estimated survival rate of 22% 5 years after the diagnosis[2,3].

Clinical presentation is heterogeneous and includes seizures, pyramidal and cranial nerves deficit, memory loss, neuropsychiatric symptoms, and signs of increased intracranial pressure; systemic manifestations like fever and night sweats are uncommon and generally preceded by neurological symptoms[4,5]. In a large study from Bataille et al[4], the mean time from the beginning of symptoms to hospital admission was 80 days. There is a strict association between EBV CNS infection and the development of PCNSL in the AIDS-population and the detection of EBV-DNA in cerebro-spinal fluid (CSF) is considered highly sensitive of CNS lymphoma. For this reason, it has been proposed as a tumor marker by Cinque et al[6]. Yanagisawa et al[7] recently proposed a cut-off of 200 copies/mL of EBV-DNA as a useful tool for the diagnosis on PCNSL, as well as for the detection of CNS involvement in AIDS-related lymphomas, with a sensitivity of 70% and a specificity of 85%.

PCNLS is usually localized in the supratentorial white matter and may consist of a solitary mass or multiple lesions; it involves more frequently the cerebral hemispheres followed by the basal ganglia and the corpus callosum[4,5,8]. Infiltration of cranial nerves, ependyma or meninges at diagnosis is common[9].

Brain computed tomography (CT)-scan has a low accuracy as lesions may appear hyper- or iso-dense, leading to false negative results[10]. Magnetic resonance imaging (MRI) is the technique of choice in the evaluation of PCNSL: lesions typically appear hyperintense on diffusion weighted (DW) MRI and hypointense on apparent diffusion coefficient (ADC) maps, as a consequence of their increased cellularity; surrounding hypointensity due to vasogenic edema may also be present. On perfusion MRI, lesions show an increased enhancement due to blood-brain barrier disruption that is generally more pronounced than in abscesses. Given the lack of neoangiogenesis in lymphomas, perfusion is lower if compared to high-grade gliomas[11]. Additionally, a peculiarity of CNS lymphoma is the prompt imaging response after administration of steroids, which depends from steroids lymphocytotoxic activity, and can lead to shrinkage or complete disappearance of enhancing nodules ("vanishing tumor")[12,13]. Imaging characteristics of CNS lymphoma depends from the immune status of the patient, reflecting probably a different etiology and aggressiveness: AIDS-related CNS lymphoma display

Corresponding Author: Claudia Chirico, MD; e-mail: claudia _ chirico@hotmail.it

more frequently (60% *vs.* 35-38%) multiple and smaller lesions, if compared to those of immunocompetent patients; in addition, a central necrosis of the lesion may be present as a consequence of rapid neoplastic growth in AIDS patients[12]. As a consequence, MRI may show lesions with a ring enhancement of the contrast medium, with a regular or irregular shape, while immunocompetent patients' contrast enhancement tends to appear homogeneous as necrosis or hemorrhage are rare before chemotherapy. Traditionally, when differential diagnosis between CNS lymphoma and toxoplasmosis was unclear after the MRI evaluation, a two weeks course of anti-toxoplasma therapy was performed, and, in absence of radiological response, brain biopsy was considered[14]. Recently, the use of thallium-201 single photon emission computed tomography (SPECT) has been proposed as a rapid and accurate tool in the differentiation between the two diseases, as thallium accumulates in the neoplastic tissue, while no uptake is present in the necrotic tissue and in abscesses. Recently a study of Hussein et al[15] reported a sensitivity of 77%, with a specificity of 81%.

CASE REPORT

In June 2016, a 40-year-old HIV-infected patient was referred to our Infectious Diseases ward for dyspnea, fatigue and cognitive impairment with memory loss. His medical history was significant for HIV infection diagnosed in 2009. He voluntarily interrupted any antiretroviral medication in 2013 and, as part of his regular monitoring, a blood test performed three months before the admission showed a CD4+ count of 12 cells/uL. After admission, chest X-ray findings and sputum microscopical examination were consistent with *P. jiroveci* pneumonia; therefore, we started administering therapy with intravenous cotrimoxazole (TMP-SMX), followed by cART initiation with abacavir sulfate/dolutegravir sodium/lamivudine plus darunavir/cobicistat.

Brain CT-scan revealed only cortical atrophy with ventricular enlargement, suggesting HIV-related encephalopathy. After three weeks, progressive worsening of the patient neurological status was observed, with the onset of walking impairment and disorientation. Brain MRI revealed multiple lesions located in both basal ganglia, in temporo-mesial regions, left occipito-mesial region, and in both peri-trigonal regions, with ring enhancement after the administration of the contrast medium (Figure 1). A diagnosis of CNS toxoplasmosis was suggested. As serology was negative (IgG/IgM) and TMP-SMX therapy did not improve the neurological status, other tests were performed and EBV-DNA (15,5491 cp/mL) was detected in CSF while a brain SPECT scan reported multiple ring enhancing lesions. High dose steroid therapy was then started but, after seven days, neither radiological nor clinical amelioration was observed. We finally performed a stereotactic-guided biopsy of the frontal lesion: histological examination revealed non Hodgkin CD20+ lymphoma and whole brain radiation therapy was started. After a month the patient was discharged in stable clinical conditions. The subsequent follow up reported a progressive amelioration of the clinical and immunological status of the patient: the last MRI performed in September 2017 showed an almost complete regression of the lesions; a lab test performed in February 2018 showed a CD4+ count of 490 cells/uL (30.3%) with stable undetectable HIV-RNA.

DISCUSSION

In our case the unusual radiological presentation of the lesions posed a challenge to the differential diagnosis with other AIDS-related conditions, especially CNS toxoplasmosis. Brain abscesses typically show ring-enhancement at MRI evaluation, but this characteristic can be shared by CNS lymphoma in presence of necrotic areas depend-

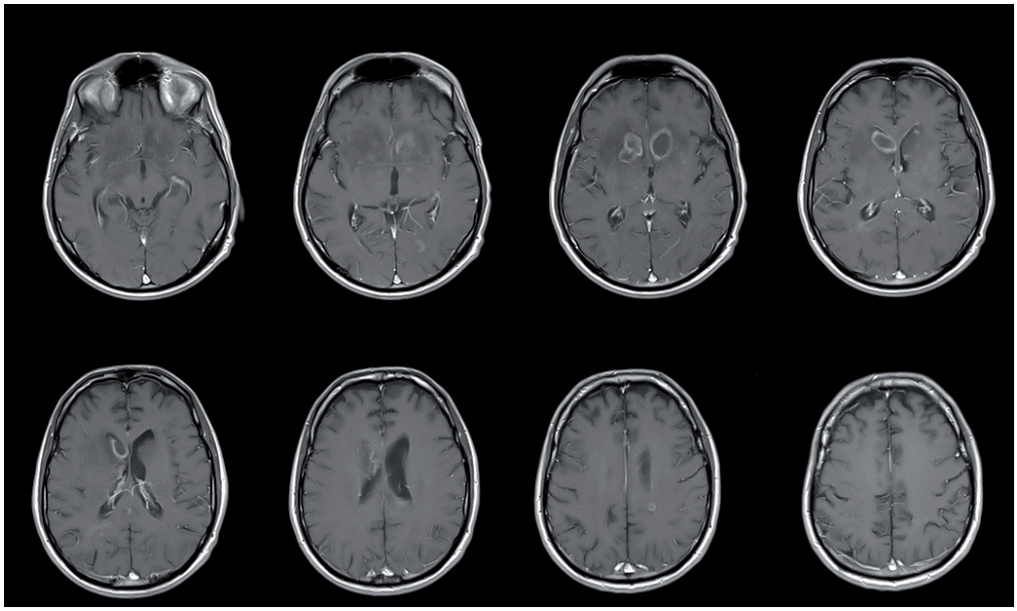

Figure 1. Multiple lesions revealed by Brain MRI.

ing from a rapid growth, which is more common in the AIDS population[12]. Unfortunately, negativity of Toxoplasma serology, as found in the reported case, has a low accuracy in immunocompromised individuals and, therefore, it does not rule out neurotoxoplasmosis diagnosis[16].

Moreover, we expected a radiological response to steroid administration, because rapid and dramatic reduction of CNS lymphoma after steroid initiation is reported in literature[12]. Since no amelioration was reported in the neurological status of the patient, we performed a brain biopsy, which allowed us to confirm our suspect.

PCNLS is an aggressive malignancy that generally occurs in the setting of a deeply compromised immune status; consequently, it is often treated with radiation therapy and ART treatment alone, even if an increasing trend in the proportion of HIV-positive patients treated with chemotherapy has been noted[17]. Prognosis is poor: estimated survival rate at five years is 22% without treatment, but reaches 40% in patients who received chemotherapy[17]. On the other hand, a mean survival time of 42 days has been reported in untreated patients[18]. Early diagnosis is therefore necessary to guarantee a chance of survival to the patient, but it can be challenging given the vast etiology of focal brain masses and heterogeneity of diseases behavior typical of the AIDS-population.

Brain biopsy has often been considered the gold standard in the characterization of brain masses. With a recent meta-analysis of 19 cohort studies, Zhang et al[19] evaluated the safety and effectiveness of stereotactic biopsy in the management of HIV-infected patients with intracranial lesions: a 92% diagnostic success rate was found with a 5.1% morbidity proportion, caused principally by hemorrhage, and a 0.7% mortality rate.

CONCLUSIONS

Nowadays, the use of advanced radiological techniques allows a high diagnostic accuracy for the definition of focal brain masses etiology in HIV-infected patients.

However, PCNLS may display atypical clinical and radiological findings in the AIDS setting, as in our case. In presence of misleading findings, brain biopsy remains a highly effective and safe procedure to achieve an early diagnosis and, as a consequence, improve prognosis.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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