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Mini Review

Discrimination between Toxoplasmic Encephalitis and Central Nervous System Lymphoma: An Updated Review

Shingen Nakamura[1*], Hirokazu Miki[2]

[1]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan; [2]Division Transfusion Medicine and Cell Therapy, Tokushima University Hospital, Tokushima, Japan

ABSTRACT

Various opportunistic infections, such as human immunodeficiency virus infections, develop in compromised hosts. The treatment options for Malignant Lymphoma (ML) and Toxoplasmic Encephalitis (TE) are completely different; therefore, discriminating between them is critical. Currently, imaging techniques such as magnetic resonance imaging, ^{201}Tl-single photon emission computed tomography, and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography and laboratory techniques such as PCR and antibody assays are used. Moreover, there are options for pathological examination using brain biopsy. However, discriminating between ML and TE remains challenging. Here, we describe an update of the discrimination methods between TE and ML.

Keywords: Human immunodeficiency virus; Toxoplasma encephalitis; Malignant lymphoma

ABBREVIATIONS

HIV: Human Immunodeficiency Virus; CNS: Central Nervous System; ML: Malignant Lymphoma; TE: Toxoplasmic Encephalitis; SPECT: Single Photon Emission Computed Tomography; FDG-PET/CT: 18F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography; CSF: Cerebrospinal Fluid; PCR: Polymerase Chain Reaction; AIDS: Acquired Immunodeficiency Syndrome; EBV: Epstein-Barr virus; PCNSL: Primary Central Nervous System Lymphoma; ^{201}Tl: ^{201}Thallium; SUV: Standardized Uptake Value

INTRODUCTION

Various opportunistic infections can develop in compromised hosts. Differential diagnosis of Central Nervous System (CNS) lesions includes Malignant Lymphoma (ML), metastatic tumors, and infectious diseases. Diseases that form space-occupying lesions are difficult to diagnose. Standard treatments for Primary CNS Lymphoma (PCNSL) and Toxoplasmic Encephalitis (TE) are quite different; therefore, their discrimination is critical. These diseases tend to develop in patients with Human Immunodeficiency Virus (HIV) infection. Therefore, the importance of considering and ruling out HIV infection when suspecting certain conditions like TE (Toxoplasma Encephalitis) or PCNSL (primary central nervous system lymphoma). Both TE and PCNSL are more likely to manifest in individuals with weakened immune systems, and HIV infection can significantly compromise the immune system. Therefore, in diagnosing TE or PCNSL, it's essential to evaluate for HIV infection as it could be a contributing factor or a potential cause for the compromised immune state leading to these conditions. By excluding HIV infection from consideration, healthcare professionals can ensure a more accurate diagnosis and appropriate management of patients presenting with symptoms suggestive of TE or PCNSL. Toxoplasmosis is transmitted to humans through the ingestion of infectious oocytes from the soil or feces of cats and insufficiently heated meat of infected animals. *Toxoplasma gondii* infection is prevalent in approximately one-third of the global population [1]. After the initial acute infection, the latent infection persists throughout the life of the host. Immunocompromised individuals, such as HIV-infected patients with CD4 count <100/μL, tend to have reactivation mostly in the CNS [2]. In addition, TE rarely occurs in immunosuppressed patients such as recipients of hematopoietic stem cell transplantations. Here, we summarize the options for diagnosing and discriminating between TE and ML in HIV-infected patients.

Correspondence to: Shingen Nakamura, Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, E-mail: shingen@tokushima-u.ac.jp

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Malignant lymphoma is known as one of the defining diseases that occur in AIDS patients. PCNSL can develop in both immunocompetent and immunosuppressed patients 63% of PCNSL cases develop in immunocompetent individuals [3]. However, individuals with AIDS have a noticeably increased risk of malignancies, such as diffuse large B-cell lymphoma (98-fold compared with the general population) and CNS lymphoma (5,000-fold) [4]. Brain biopsy is the gold standard method for diagnosis; however, it is invasive and is not possible to perform for all locations. Additionally, TE is likely to develop in HIV-infected individuals; therefore, it is important to differentiate between TE and PCNSL. Furthermore, at the point of treatment, anti-parasitic therapy is the best treatment for TE, and HD-MTX-based systemic chemotherapy is essential for PCNSL. A study showed that the median Overall Survival (OS) was 0.3 years in HIV-associated PCNSL, both with and without chemotherapy (when analyzed limited to patients who received chemotherapy, the median OS was 1.5 years) [5]. Therefore, diagnostic delay leads to worse prognosis in HIV-associated PCNSL.

LITERATURE REVIEW

Here, we summarize the options for diagnosing and discriminating between TE and ML in HIV-infected patients (Table1).

Imaging

CNS lesions in patients with AIDS may include PCNSL, mycobacterial infection, cytomegalovirus encephalitis, cryptococcosis, bacterial abscesses, metastatic cancer, and, uncommonly, progressive multifocal leukoencephalopathy. Brain magnetic resonance imaging is often performed as a first-line diagnostic imaging modality. Both TE and PCNSL lesions are enhanced by contrast agents and appear ring shaped. Therefore, other modalities must be considered for more accurate discrimination (Table1).

Single Photon Emission Computed Tomography (SPECT)

^{201}Tl-SPECT is frequently performed to differentiate CNS lesions. Some studies have reported discrimination based on the uptake of Tl, CNS mass number/size, and other parameters in combination. Miller et al. reported a discrimination method for patients with AIDS using a combination of ^{201}Tl uptake and number of CNS lesions. Isolated lesions with the uptake of ^{201}Tl indicated PCNSL, whereas lesions without the uptake indicated TE. In patients with multiple lesions and high ^{201}Tl uptake (uptake ratio>2.9), all lesions were of PCNSL, and ^{201}Tl uptake of all lesions in patients with TE was 2.1 [6]. Lorberboym et al. reported discrimination between PCNSL and TE by combining the uptake and retention indices of ^{201}Tl [7]. If the lesion had accumulated ^{201}Tl in the early phase, a low retention index suggested a benign lesion, and the retention index, in addition to the early uptake of ^{201}Tl, increased the specificity of malignant lesions [7]. Robert TC, et al. [8], reported differentiation between lesion size and Tl index; the Tl index is a significant predictor of malignancy in lesions ≥ 2 cm (P<0 .01) with 100% sensitivity and 89% specificity but is not a significant predictor of malignancy in lesions <2 cm. However, there are some exceptions. We

Category	Modality	Advantage	Disadvantage
Imaging	MRI	The basis for differentiating various diseases	Low specificity
	^{201}Tl-SPECT	Useful for discrimination between tumor or others	Some exceptions
	FDG-PET/CT	SUV_{max} is useful	Exposed to radiation
CSF test	*T. gondii* PCR	High specificity	Low availability
	EBV-DNA PCR	Useful for diagnosis of PCNSL	None
Serological test	Anti-*T. gondii* IgG, IgM	Easily conducted	Low sensitivity
Therapeutic diagnosis	Anti-*T. gondii* treatment	Possibility with avoidance of subsequent brain biopsy	Possibility of delayed diagnosis of PCNSL
Brain biopsy	Histological examination	Gold standard	May be difficult to find oocysts
	Anti-*T. gondii* PCR	High specificity	Low availability

Table1: Options for discrimination between TE and PCNSL. **Note:** Magnetic resonance imaging (MRI); Single Photon Emission Computed Tomography (SPECT); ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT); Cerebrospinal Fluid (CSF); Polymerase Chain Reaction (PCR); Acquired Immunodeficiency Syndrome (AIDS); Epstein-Barr virus (EBV); Primary Central Nervous System Lymphoma (PCNSL); ^{201}Thallium (^{201}Tl); Standardized Uptake Value (SUV).

experienced a case with HIV infection with multiple brain lesions [9]. One of the CNS lesions had high ^{201}Tl uptake with a T/N ratio of 3.034 and a retention index of 0.9, while the others had low ^{201}Tl uptake and retention; therefore, we suspected synchronous development of PCNSL with TE. We biopsied both the high- and low-retention index lesions, but they were eventually diagnosed as TE [9]. Discrimination between ML and TE remains challenging in SPECT.

^{18}F-Fluorodeoxyglucose-Positron Emission Tomography/ Computed Tomography (FDG-PET/CT)

FDG-PET/CT is widely used in clinical practice, particularly in oncology. FDG-PET/CT is useful in discriminating between PCNSL and TE. A previous study reported that the usefulness of the Standardized Uptake Value $(SUV)_{max}$ of the lesion was significantly lower in cerebral toxoplasmosis or tuberculoma than in PCNSL $(SUV)_{max}$, 3.5 (1.9-5.8) *vs.* 18.8 (12.4-29.9) [10].

DISCUSION

Cerebrospinal Fluid (CSF) test

Polymerase Chain Reaction (PCR) of CSF has high specificity (100%) but low sensitivity (50%-60%) for detecting toxoplasmosis [11,12]. However, the availability of PCR tests may be limited in clinical practice. A study reported a combined approach using ^{201}Tl-SPECT and Epstein Barr Virus (EBV) DNA in the CSF of 13 patients with PCNSL and 18 patients without tumors [13]. In PCNSL patients, a ^{201}Tl lesion/background ratio <1.95 was found only in one case, and EBV DNA was never detected in patients without neoplasms; therefore, the presence of increased uptake and/or positive EBV DNA had 100% sensitivity and 100% negative predictive value for the diagnosis of PCNSL [13]. Therefore, PCR testing for EBV DNA and Toxoplasma may aid in the final diagnosis.

Serological test

In most patients with reactivation of Toxoplasma, both serum IgM and IgG antibodies against *Toxoplasma gondii* are positive; however, false-negative serological IgM results rarely occur and are typically observed in patients who are significantly immunocompromised [14]. Moreover, the absence of IgG antibodies does not completely exclude the possibility of TE in immunocompromised individuals.

Therapeutic diagnosis

Empiric diagnostic treatment is performed if the patient has a CD4 count of <100/μL, without prophylaxis for toxoplasmosis, with compatible clinical features, positive *T. gondii* IgG antibody, and typical brain imaging, such as multiple ring-enhancing lesions. If these criteria are present, there is a 90% probability that the diagnosis is TE [15,16]. A study reported on 136 consecutive patients with HIV infection who presented with focal CNS lesions [17]. Following 3 weeks of empiric therapy for TE, brain biopsy was performed in patients with progression. The probability of TE was 0.87 in Toxoplasma-seropositive patients with a mass effect, who were not treated with trimethoprim-sulfamethoxazole, but only 0.59 for those receiving prophylaxis. Thus, empirical therapy for toxoplasmosis may be considered as an alternative method to discriminate between PCNSL and TE in patients with characteristic radiographic findings.

Brain biopsy

Brain biopsy is the gold standard method for the diagnosis of focal lesions in the CNS; however, it is an invasive procedure that is influenced by the location of the lesions and whether a brain biopsy can be performed [17]. Therefore, rapid diagnostic procedures are required to differentiate between PCNSL and TE. Moreover, brain biopsies revealed inflammatory cell infiltration with a few toxoplasmas in our case [6]. Therefore, in addition to histological examination, PCR of biopsy specimens can aid in the diagnosis of TE.

CONCLUSION

We described the discrimination between TE and PCNSL diagnosis. These diseases develop in patients with HIV infection, and the status of HIV infection should be confirmed when TE or PCNSL is suspected. If the definitive diagnosis of CNS lesions in patients with HIV infection is uncertain, a combination of multiple tests, including MRI, SPECT, FDG-PET/CT, CSF test, PCR test, anti-parasitic therapy for TE (therapeutic diagnosis), and brain biopsy should be performed as soon as possible, which may aid in an accurate diagnosis and better prognosis.

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CONFLICTS OF INTEREST

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