Chinese Medical Journal®

Three acquired immunodeficiency syndrome patients with central nervous system infection: diagnostic approach and outcome of treatment

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The patients with acquired immunodeficiency syndrome (AIDS) are prone to opportunistic infections due to immune deficiencies. Because the AIDS virus is neuropathic, 10% of AIDS patients first manifested central nervous system (CNS) symptoms.[1] More than 40% of untreated AIDS patients will develop CNS diseases.[2] The diagnosis and treatment for AIDS complicated with intracranial lesions are mainly based on clinical experience and laboratory tests. If necessary, brain biopsies were taken into consideration to help to diagnose and choose a suitable therapy. In clinic practice, to get a specific diagnosis is very difficult. To further analyze the clinical features of such patients and to provide some suggestions for the clinical diagnosis and treatments, we retrospectively analyzed three AIDS cases with CNS infection who attended the Peking Union Medical College Hospital.

Total 442 cases were admitted to Chinese Academy of Medical Sciences Peking Union Medical College Hospital with a clear diagnosis of AIDS from 1985 to 2017, and there were three cases diagnosed as intracranial infection confirmed by cerebrospinal fluid (CSF) analysis and brain biopsy. Since routine antiretroviral therapy and empirical treatment did not improve the patient's outcome of disease, we performed the brain biopsy to obtain a specific diagnosis. This study was approved by the Ethics Committee of Peking Union Medical College Hospital and was performed in accordance with the *Declaration of Helsinki*.

All three patients developed symptoms of focal neurological dysfunction (such as dysphonia, paraesthesia, or extremities weakness). In terms of serology and CSF examination, there was a positive cytomegalovirus (CMV)-IgG/IgM test in case 1, serology for CMV-IgG was positive in case 2 (combined with a bit of high protein level in CSF test) and CSF acid-fast staining was positive in case 3. The brain magnetic resonance imaging (MRI) of three cases revealed multiple abnormal intracranial signals. Sites of biopsy target depend on preoperative imaging (left/right frontal lobe in two cases, left frontal-temporal lobe in the other case). Three patients included two males and one female, with a mean age of 36 years.

In the first case, a 47-year-old woman was diagnosed with AIDS in the setting of weight loss in 2006. The histopathology confirmed progressive multifocal leukoencephalopathy combined with toxoplasma encephalopathy. Special staining for *Toxoplasma gondii*: Hexamine silver (+), Periodic Acid-Schiff stain (PAS) (+) [Figure 1]; highly active antiretroviral therapy (HAART) and anti-*Toxoplasma gondii* treatment were applied [Table 1]. The patient was discharged without significant symptom improvement.

In the second case, a 25-year-old man presented with asyndesis and motor disturbance of the right limb for 3 months. The brain biopsy smear showed pairs of gram-positive cocci and gram-negative bacilli. HAART and Anti-infective treatment were applied [Table 1]. He was discharged with symptoms of improvement.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000507

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Chinese Medical Journal 2019;132(22)

Received: 25-05-2019 **Edited by:** Li-Min Chen

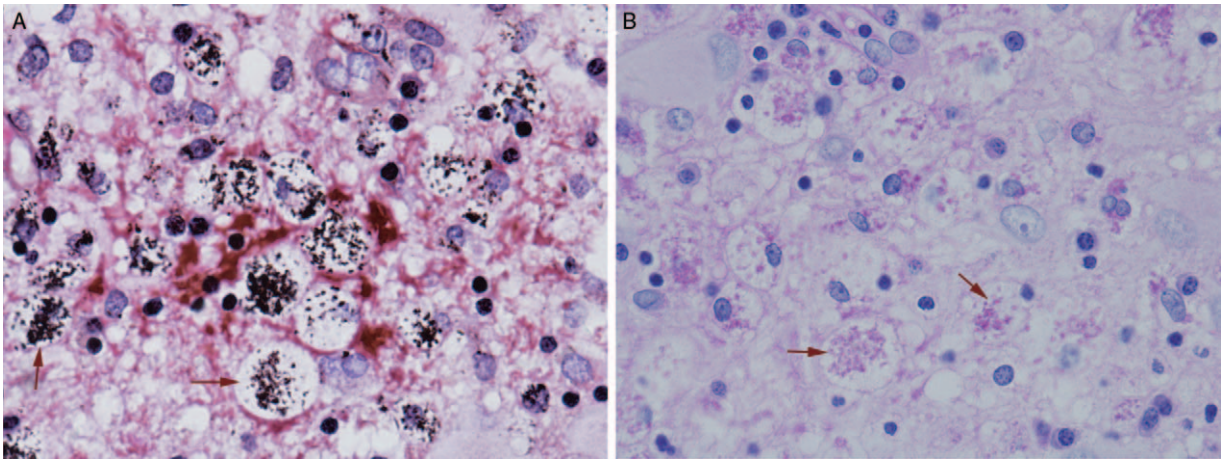

Figure 1: The rough granular matters (arrows) presented in the cytoplasm which were considered the *Toxoplasma gondii* (A, hexamine silver staining, original magnification × 40; B, periodic acid-schiff staining, original magnification × 40).

Table 1: Three AIDS cases with intracranial infection by anti-virus and anti-infective treatment.

Case No.	HAART	Anti-infective treatment	Outcomes of focal neurological symptom
1	Lamivudine +Stavudine+ Nevirapine	TMP+ Clindamycin+ Azithromycin+ SMZco	No significant improvement
2	Efavirdine + Lamivudine + Stavudine	Ceftazidime+ Norvancomycin	Clinical symptoms improved
3	Lamivudine + Stavudine + Nevirapine	Isoniazid+ Rifampin+ Pyrazinamide+ Ethambutol	Clinical symptoms improved

AIDS: Acquired immunodeficiency syndrome; HAART: Highly active antiretroviral therapy; SMZco: Compound sulfamethoxazole dispersible tablet; TMP: Trimethoprim.

In the third case, a 37-year-old man was admitted with fever and headache in 2013. We found his sputum acid-fast staining was positive. Later, the CSF acid-fast staining was also confirmed positive which obtained from the second CSF test. Furthermore, his CSF bacterial culture showed *Staphylococcus hominis* positive. The histopathology result is unspecific. HAART and anti-tuberculosis treatment were applied [Table 1]. The patient was discharged with significant symptoms of improvement.

AIDS patients complicated with meningeal tuberculosis are relatively rare. Tuberculous meningitis is the most severe form of tuberculosis specifically in individuals co-infected with human immunodeficiency virus (HIV). Typically, the CSF analysis shows elevated protein, low glucose, and elevated mononuclear pleocytosis in meningeal tuberculosis. Due to a low burden of mycobacteria in one CSF samples, we obtained CSF acid-fast staining (+) from the second CSF test after we detected the sputum acid-fast staining (+). Due to the good outcome that our patient accepted the 4-drug anti-tuberculous therapy, we believed such a result strongly supported the diagnose of tubercular meningitis in a reverse side, which the conclusion based on the fact that most non-mycobacterium tuberculosis is resistant to common anti-mycobacterial drugs.

When clinical symptoms and imaging findings were not significantly improved with empirical treatment for intracranial lesions, a tissue diagnosis should be attempted if possible. Rosenow and colleagues performed 246 cases of stereotactic brain biopsy in AIDS patients with intracranial lesions, concluded that the positive rate of pathological diagnosis was 92.3%.[3] Zibly *et al* reported the positive rate of pathological diagnosis was 93.75%.[4] Though these data confirmed the usefulness of biopsy in patients with AIDS with its wide range of associated cerebral lesions (diagnostic accuracy often greater than 90%), there are still some brain biopsy results in either descriptive diagnosis only that were nondiagnostic. In our first brain biopsy, the special staining (Hexamine silver and PAS) for *Toxoplasma gondii* were exclusively positive, we considered that it would be better to perform the immunohistochemistry, *in situ* hybridization or polymerase chain reaction for further evidence of the diagnosis. The other two cases of biopsies we reported only indicated infection without a specific diagnosis, more evidence we obtained were from tissue biopsy smears and anti-acid staining of cerebrospinal fluid.

The early introduction of highly effective antiretroviral therapy for AIDS patients has a positive effect both in controlling the mortality and slowing the spread of HIV.[5] The MRI findings of the first case we reported was consistent with AIDS encephalopathy, although she received early aggressive treatment about HAART, there is no obvious improvement in her neurocognitive functioning. This may have a great relationship with her simultaneous

comorbidities of toxoplasma encephalopathy and progressive multifocal leukoencephalopathy. Besides, the blood-brain barrier limits the access of antiretrovirals drugs to the CNS. So, we recommend a high-dose and high-tolerant antiretroviral treatment containing three or four types of drugs in the early stages of infection.

In clinical practice, a brain biopsy cannot completely replace imaging findings and serology/cerebrospinal fluid analysis. For simultaneous comorbidities of CNS infection, it is often limited in the improvement of neurological deficit symptoms even if the patient received adequate antiviral and anti-infective therapy. Therefore, the active intervention including multidisciplinary cooperation and multiple diagnostic techniques, such as biopsy, may have implications to improve the outcomes of AIDS patients complicated with CNS infection.

Conflicts of interest

None.

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How to cite this article: Chen YH, Chang JB, Wei JJ, Lyu W, Yu SN, Ma BT, Wu H, Zhang X, Lian W, Ma WB, Wang TT, Li TS, Wang RZ. Three acquired immunodeficiency syndrome patients with central nervous system infection: diagnostic approach and outcome of treatment. Chin Med J 2019;132:2754–2756. doi: 10.1097/CM9.0000000000000507