CASE REPORT

Clinical presentation and outcome of progressive multifocal leukoencephalopathy in a person living with HIV - review of three cases in North-Western Malaysia

Lim Zi Xiong, MRCP, Jerome Gan Jheng Rhong, MRCP, Saw Li Sean, MRCP

Department of Medicine, Hospital Pulau Pinang, Malaysia

SUMMARY

We reviewed the clinical presentations and outcomes of three cases of progressive multifocal leukoencephalopathy (PML) in a person living with HIV in our setting and compare with general literature review. The clinical presentations can vary among individuals but most invariably will have certain neurological symptoms. The diagnosis of PML in all the three patients are done through clinical and radiological approach. The outcomes are generally poor. The mainstay of PML in HIV patients is to start antiretroviral therapy (ART), despite the poor outcome of PML in the patients. The purpose of The highly active antiretroviral therapy (HAART) is to prevent any other opportunistic infections from occurring in HIV patients. Background and objectives: To review and compare the clinical presentations and outcomes of Progressive Multifocal Leukoencephalopathy (PML) in a Person living with HIV (PLHIV) at Penang General Hospital (PGH), Pulau Pinang.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a form of demyelinating disease of the central nervous system (CNS), caused by infection of human polyomavirus 2 (JC virus).. It occurs almost exclusively in immunosuppressed individuals. There has been a dramatic evolution in how PML is diagnosed over the years with clinical, laboratory, radiological and tissue biopsy procedures. Its incidence has reduced dramatically with the invention of ART; however, the outcomes remain poor. The purpose of this study is to review the clinical presentations and outcomes of PML patients in Penang General Hospital, which has longed serves as a reference hospital in the northern part of Malaysia. In these case studies, we are using clinical and radiological method to explain the clinical finding and the outcomes of PML in three different HIV patients.

CASE PRESENTATION

Case 1

A 45-year-old Indian man, presented with weight loss and neurological symptoms (unsteady gait, slurring of speech and weakness over the left arms) in July 2022 for 6 months. He was initially treated as hemiplegic stroke. Bur due to extreme weight loss, he was tested for HIV test. He was diagnosed with HIV during admission (CD4: 18 cells/mm^3, VL: 131417 copies/ml during presentation). After discharge, he had been semi dependent with residual weakness in the left side of his body. Initial plan was to start him on HAART in July 2022; however, it was delayed as patient admitted again for COVID pneumonia in August 2022 and septic shock with pneumonia in September 2022. In October 2022, he was admitted again due to worsening lethargy and inability to ambulate for 2 weeks. During admission in October 2022, he had spastic tetraplegia with bilateral CN VII nerve palsy. He is now wheelchair bound and ADL dependent.

Case 2

A 63-year-old Chinese man with hypertension, presented with fever, weight loss, loss of appetite and respiratory symptoms (breathlessness, reduced effort tolerance) in September 2021. He underwent CECT TAP and it showed an infected lung nodule. HIV test was positive (CD 4: 36 cells/mm^3, VL 798982 copies/ml), lumbar puncture was performed as he developed high intracranial pressure. His CSF C & S and blood C & S showed cryptococcal neoformans. He was given intensive antifungal flucytosine and fluconazole. As he had persistent diarrhoea, a colonoscopy was done, and it showed extensive ileocolonic ulcers. The biopsy results showed cytomegalovirus colitis. He was subsequently treated with IV ganciclovir for 2 weeks. After discharge, he immediately started on ART. He had multiple admissions from September 2021 till September 2022 for frequent chest infections and anaemia. He had a few episodes of fittings in between September and October 2022. He was diagnosed with PML after CT and MRI brain. Despite started on HAART, he never improved from PML. He is now bed bound and ADL dependent.

Case 3

A 54-year-old Chinese woman, presented with fever, headache and neurological symptoms in February 2018. Her initial neurological symptoms include altered behaviour, unilateral body weakness and facial asymmetry. Her HIV test turned out positive (CD 4: 158.3 cells/mm^3, VL: 181 copies/ml). With her significant clinical symptoms, she was initially treated as meningitis and cerebral toxoplasmosis. The meningitis and cerebral toxoplasmosis treatment were stopped as there were no signs of clinical improvement despite a week of antibiotics. Her CSF investigations were all negative (culture/HSV/CMV/TB). She was diagnosed with PML after an MRI was done. She was initiated on ART therapy subsequently. She remains bed bound to date and ADL dependent despite given ART.

This article was accepted: 02 September 2023
Corresponding Author: Ingrid Ting Pao Lin
Email: ingrid_tpl15@hotmail.com

Table I:

Characteristic	Case 1	Case 2	Case 3
Age	46	63	54
Underlying comorbidities	No known medical illness	Hypertension	No known medical illness
cART	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON
CD4 count	18 cells/mm³ (on 15/07/22)	36 cells/ mm³ (on 03/10/21)	158 cells/ mm³ (26/2/18)
Clinical manifestation			
- Headache	No	No	Yes
- Fever	No	No	Yes
- Neck stiffness	No	No	No
- Impaired consciousness	No	Yes	Yes
- Focal neurological deficit	Yes	Yes	Yes
Serum toxoplasmosis	IgM/IgG non-reactive	IgM/IgG non-reactiv	IgM NR/IgG Reactive
CSF parameters			
- Opening pressure	-	-	-
- Cell count	Nil	Nil	Nil
- Glucose	3.7 mmol/L	2.6 mmol/L	2.92mmol/L
- Protein	0.67 g/L	0.38 g/L	0.49g/L
- Culture & Sensitivity	No Growth	No Growth	No Growth
- India Ink	Negative	Negative	Negative
Neuroimaging	Multiple T2W/FLAIR hyperintensities in bilateral subcortical and deep white matter at bilateral frontal, bilateral parietal lobe, bilateral external capsule, bilateral internal capsule, bilateral putamen, bilateral globus pallidus and midbrain	T2W/FLAIR high signal intensity in both cerebellar hemisphere (right > left), right side of midbrain, pons and left cerebellum	Low T1 and high T2 and FLAIR signal lesions in the white matter of the right temporal lobe and left medial temporal lobe and lateral dorsal aspect of the right midbrain. No focal enhancing lesion or meningeal enhancement
Outcome, GOS	3	3	3

Table II:

Antiviral therapy **1. JCV cell entry inhibitor**		**Immune response modulator** **1. Cytokines**		**Immunisation** **1. Passive immunisation**	
Chlorpromazine Citalopram	Block serotonin receptors	IFN α	Stimulate innate, adaptive immune response	Recombinant anti JCV VP 1 monoclonal antibodies	To neutralise JCV
IL- 2 Mirtazapine	Stimulate T cell lymphocyte growth		JCV specific cytotoxic T lymphocytes	Lysis, clearance of JCV JCV infected cells	
IL- 7 Risperidone	Stimulate lymphoid lineage development				
1. DNA replication inhibitors		**1. Inflammation inhibitors**		**1. Active immunisation**	
Cidofovir	Inhibit viral DNA polymerase	Maraviroc	Blocks CCR 5 mediated tissue inflammation	IL 7 + JCV VP 1 vaccine	JCV capsid protein with recombinant IL 7 to boost JCV T cell response
Cytarabine Ganciclovir Leflunomide	Inhibit DNA, RNA polymerase, nucleotide reductase	Inhibit viral DNA polymerase Inhibit mitochondrial enzyme	Glucocorticoid	General immune system suppression	

The above Table I compares the background history, clinical presentation, and radiological findings of our three PML patients. The outcome of all the three patients is poor with a disability requires daily care. Glasgow Outcome Scale (GOS) is an objective description or scale to measure the outcome of patient with brain injury.

DISCUSSION

PML is a demyelinating disease of the CNS, particularly the white matter. It is caused by reactivation of JC virus.[1] JC virus exposure is usually asymptomatic and occurs in childhood or adolescence. The JC virus only infects humans, where it resides in latent form in various tissues, including the brain.[2] A JC virus spreads through interpersonal contact or by fomites in the environment to the oropharynx, where it replicates and produces variants.[3] Nearly 85% of the cases of PML associated with HIV infection have CD4 counts below 200 cells/mm^3. It can occur at the initial presentation of HIV or during immune recovery following ART initiation. JC virus incidence has been reported to be low in India and Africa (possibly due to diagnostic limitations and differences between isolates). The most common symptoms of PML are motor weakness (hemiparesis/hemiplegia), impaired vision (homonymous hemianopia) and changes in mental status (personality changes, memory loss, emotional lability, and dementia).[4] Rarer forms can present with movement disorders instead of focal neurological deficits. The diagnosis of PML can be done, either based on a brain biopsy or by clinical and imaging features. Brain biopsy is the most accurate method to diagnose PML, however it is invasive and comes with complications of post biopsy haemorrhage.[5] There is a chance of a false negative result if the sample obtained are necrotic brain tissues.[6] The histopathology of PML tissue biopsy usually exhibits triad of demyelination, enlarged oligodendrocyte nuclei and bizarre astrocytes.[7] PML can also be diagnosed through clinical and radiological findings combined with JCV DNA virus via PCR (from CSF). JVV PCR is one of the sensitive tests that can be utilised. It is highly specific (92-99%) and sensitive (74-93%).[8] PCR results may be falsely negative if the viral counts are low in the CSF.[9] We have able to diagnose the patients in these three cases through the approach of clinical manifestation and radiological presentation. We have limited capabilities to be able to run JCV DNA PCR in our setting due to high cost of the test. MRI brain with multisequence protocol allows us to differentiate PML by a distinctive demyelination pattern (hyperintense on T2 weighted MRI and hypointense on T1 weighted MRIs). There is a direct correlation between PML and HIV.[10] HAART is currently the mainstay of PML treatment and has been shown to reduce PML mortality in HIV patients.[11] The prognosis depends on the initial CD4 count and compliance to HAART.[12] HAART can improve PML outcomes in person living with HIV (PLHIV), but it can also unmask inflammatory PML during immune reconstitution (IRIS), which is associated with worsen clinical and radiological outcomes. The exact mechanism of IRIS is not fully understood, and more research is needed to improve the treatment of IRIS in these high-risk patients. The common treatment of IRIS involves a usage of high dose of corticosteroids that can help in suppress the exaggerated immune mechanism after the introduction of HAART. These PML IRIS patients generally have poor outcomes despite being treated with ART and high dose corticosteroid.[13] There are a few studies focus on finding the effective anti JCV treatment and PML prophylaxis. To date, there are no absolute and definite treatment to PML. These treatments are made up of antiviral agent, immune response modulator and immunisation. The antiviral agent is designed to prevent the JCV entry and to prevent further DNA replication. Immune modulators function to restore the protective defence mechanism and to inhibit exaggerated response in PML-IRIS. Immunisation strategies is a form of passive immunisation meant to introduce the monoclonal antibodies generated from human donors. The treatments are not widely recognised as there is a limitation of study size. The treatments are also very dose dependent as it needs higher doses to reach the blood–brain barrier.

The above Table II further explains the different agents and mechanisms that are studied before but not widely used due to limitation of sample populations.

CONCLUSION

The outcome of the above three cases is poor, in keeping with most literature reviews regarding the outcome of person living with HIV (PLHIV) with progressive multifocal leukoencephalopathy (PML). All of them were bed bound and ADL independent (with GOS 3) despite started on antiretroviral therapy (ART). It is possibly and likely due to the late presentation and late diagnosis of illness. It is always challenging when come to diagnose brain infection in a HIV patient especially PML infection. There are other CNS opportunistic infections that healthcare providers need to think of before concluding for what possible brain infection a patient might have. These case studies are to raise awareness among healthcare providers regarding the clinical presentation, outcome and treatment options in a HIV patient living with PML. ART remains the upmost important treatment in the light of PML and HIV infection. As PML infection ends with a poor outcome, many research and studies are done and performed widely to find the cure for PML. In the hope of near future, many useful and definite therapy will surface to help those HIV living with PML patient especially with these antiviral agent, immunomodulator and passive immunisation.

REFERENCES

1. Berger, JR, Aksamit, AJ, Clifford, DB, Davis, L, Koralnik, IJ, Sejvar, JJ et al. PML diagnostic criteria. Neurol 80(15): 1430-8.
2. Paz, SP, Branco, L, Pereira, MA, Spessotto, C, Fragoso, YD. Systematic review of the published data on the worldwide prevalence of John Cunningham virus in patients with multiple sclerosis and neuromyelitis optica. Epidemiol Health 2018; 40: e2018001.
3. Cortese, I, Reich, DS, Nath, A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol 2020; 17(1): 37-51.
4. Berger, JR. The clinical features of PML. Cleve Clin J Med 2011; 78(11 suppl 2): S8-S12.
5. Schuette, AJ, Taub, JS, Hadjipanayis, CG, Olson, JJ. Open biopsy in patients with acute progressive neurologic decline and absence of mass lesion. Neurol 2010; 75(5): 419-24.
6. Wang, M, Zhang, Z, Shi, J, Liu, H, Zhang, B, Yan, J. Progressive multifocal leukoencephalopathy in an HIV patient was diagnosed by 3 times lumbar punctures and 2 times brain biopsies. J NeuroVirol 2020; 26(6): 952-6.

7. Chalkley, JJ, Berger, JR. Progressive Multifocal Leukoencephalopathy in multiple sclerosis. Curr Neurol Neurosci Rep 2013; 13(12).
8. Lee, S, Ko, H, Kim, S, Lee, Y, Son, B. Progressive multifocal leukoencephalopathy diagnosed by brain biopsy, not by the DNA test for JC virus. Asian J Neurosurg 2019; 14(1): 240-44.
9. Landry, ML, Eid, T, Bannykh, S, Major, E. False negative PCR despite high levels of JC virus DNA in spinal fluid: Implications for diagnostic testing. J Clin Virol 2008; 43(2): 247-49.
10. Pavlovic, D, Patera, AC, Nyberg, F, Gerber, M, Liu, M. Progressive multifocal leukoencephalopathy: Current treatment options and future perspectives. Ther. Adv. Neurol. Disord 2015; 8(6); 255-73.
11. Cinque, P, Koralnik, IJ, Gerevini, S, Miro, JM, Price, RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis 2009; 9(10): 625-36.
12. Khanna, N, Elzi, L, Mueller, N, Garzoni, C, Cavassini, M, Fux, C et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV cohort study. Clin Infec Dis 2009; 48(10): 1459-66.
13. Eskut, N, Inci, I, Ozdemir, H, Gedizlioglu, M, Tosun, S. This time in a reverse order: Seizure, progressive multifocal leukoencephalopathy, and then AIDS was diagnosed. Neurol India 2021; 69(3): 768.