CASE REPORT

Progressive multifocal leukoencephalopathy in HIV with atypical presentation and prognostic outcome causing diagnostic dilemma: a case report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by John Cunningham virus (JCV) that affects immunocompromised individuals, particularly human immunodeficiency virus (HIV)-positive. Classical symptoms of PML alter mental status, causing paralysis and diplopia. Bizarre presentations, such as seizures and personality change, are rare in PML, which may lead to a delay in diagnosis and treatment. A 31-year-old HIV-positive Malay man on antiretroviral therapy (ART), presented with two episodes of generalized tonic-clonic seizures. First brain MRI showed a solitary right frontal lobe lesion, for which brain biopsy revealed inflammatory infective process with normal cerebrospinal fluid (CSF) examination, and led to diagnosis of primary lymphoma. Four months later, the patient developed progressive personality changes, reduced cognitive function, and left upper limb paralysis. Second brain MRI showed progression of asymmetrical distribution of white matter changes involving sub-cortical, deep, and periventricular area, a classical feature of PML. ART and intensive neuro-rehabilitation were continued, and the patient's condition slowly improved; however, cognitive function remained affected.

Our case is the first reported case of PML with HIV, who survived six years after diagnosis despite initial diagnostic dilemma and poor prognostic factors. This case illustrates that survival is possible with compliance with ART and intensive rehabilitation.

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Key words: human immunodeficiency virus (HIV), progressive multifocal leukoencephalopathy (PML), antiretroviral therapy (ART).

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare, demyelinating disease with insidious onset caused by John Cunningham virus (JCV) that affects individuals with immunocompromised conditions [1-4]. Named after the initials of the first infected patient [4], it is one of the most feared condition associated with human immunodeficiency virus (HIV) due to fatal complications [5]. PML affects 1-5%

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of HIV and acquired immunodeficiency syndrome (AIDS) patients [4, 5]. It is associated with high mortality rate (18%), especially before commencement of antiretroviral therapy (ART) [6], and important cause of morbidity in AIDS [5]. The virus destroys oligodendrocytes and myelin sheath, leading to demyelination and cavitary necrosis [1, 4]. Initial symptoms include focal and coordination deficits, hemiplegia, and memory and cognitive impairment, while headache, seizures, neck stiffness, and personality change are infrequent presentations [2, 3]. Atypical presentation may lead to delay in diagnosis and treatment.

Here, we presented a case of newly diagnosed HIV and AIDS with high viral load and low CD4 count, presenting with bizarre and atypical symptoms of PML. Four months later, the patient was finally diagnosed with PML based on classical features seen on MRI. ART was continued, and the patient survived despite severe neurologic sequalae.

Case description

A 31-year-old man presented to emergency department (ED) due to two episodes of generalized tonic-clonic seizures, which lasted for five minutes in September 2016. He was started on ART after being diagnosed with HIV, concurrent pulmonary tuberculosis, and hepatitis B infection one month prior. Upon assessment at ED, he was alert,

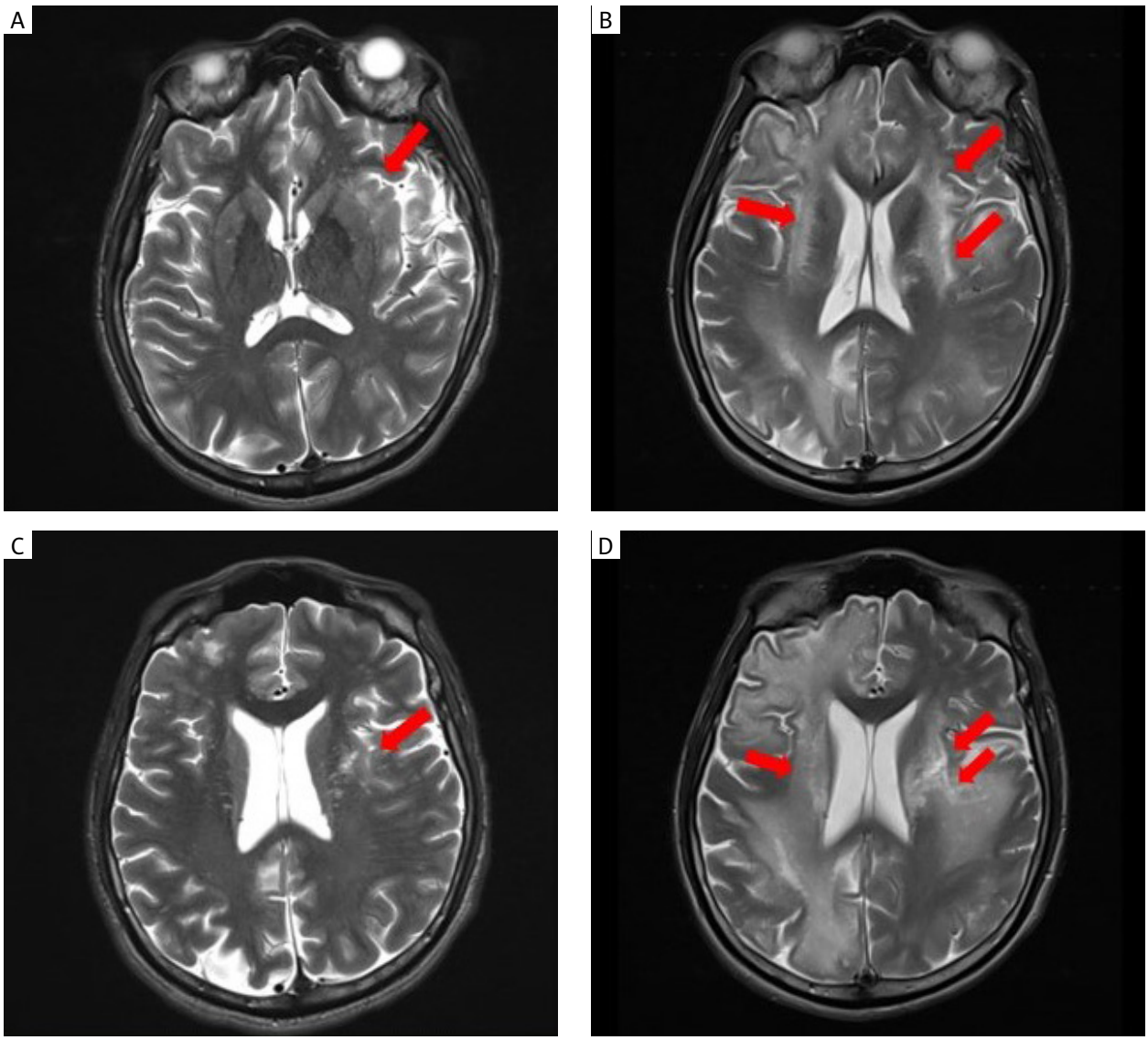

Figure 1. A, C) Brain magnetic resonance imaging (MRI) on the first presentation. **B, D**) Brain MRI after 4 months from presentation with diagnostic findings of progressive multifocal leukoencephalopathy. Abnormal signal in the white matter with asymmetrical distribution at both frontal, right parietal, and left temporal lobes, which demonstrated high signal on T2 (**A, C**) significantly increased involving sub-cortical and deep cerebral white matter with asymmetrical distribution (**B, D**), compared with the first MRI. The signal was visualized at both frontoparietal lobes, left temporal lobe, and periventricular area (**B, D**)

coherent with stable vital signs, and there was no neurological deficit. A cerebrospinal fluid (CSF) analysis showed low total protein of 18.9 mg/dl, normal glucose of 70 mg/dl, negative cryptococcal antigen test, and negative tuberculosis polymerase chain reaction (PCR) test. Herpes simplex virus (HSV) serology, latex agglutination test, viral culture, and JCV PCR were not evaluated. Viral culture and JCV PCR were not done because there were not available in our facility. Bacterial and fungal cultures were negative. First magnetic resonance imaging (MRI) of the brain revealed an abnormal signal in the white matter, with asymmetrical distribution in both frontal, right parietal, and left temporal lobes, which demonstrated low signal on T1, high signal on T2, and mixed low to high signal on fluid attenuated inversion recovery (FLAIR). Some of the white matter changes were confluent, and some presented with spongiform appearances. Post-contrast, the lesion was solitary avid and homogeneously enhanced at the right frontal lobe measuring 1.2 cm x 1.3 cm, with mild perilesional oedema (Figure 1). A preliminary diagnosis of primary CNS lymphoma was made based on similar features shown on MRI; in order to confirm the diagnosis further, a biopsy of the brain lesion was scheduled a month later. During in-patient stay, the patient was started on tapering dose of oral prednisolone to reduce perilesional oedema seen on MRI, and epilim 200 mg twice a day orally was initiated as antiepileptic treatment.

In November 2016, the patient presented with unusual behavior and progressive left upper limb weakness. He was irritable and angry, especially towards the evening, and was described as being hysterical by his mother. During the day, he was calm. There was no physical aggression, hallucination, or delusional thoughts. He was noted to be forgetful, with poor judgement at work, and found to be unfit to continue working. His scheduled brain biopsy, which was done in November 2019, showed reactive astrocytes, proliferation of small vessels, and infiltration by a mixture of lymphocytes, histiocytes, and occasional plasma cells (Figure 2). There was perivascular lymphocytic cuffing typically seen in brain lymphoma; however, immunohistochemical studies revealed a mixture of reactive B and T lymphocytes. Intra-nuclear inclusions indicating JC virus were not identified. The histopathology concluded features of inflammation or infective process with no evidence of lymphoma cells, excluding the working diagnosis of a primary lymphoma made earlier. By December 2016, the patient

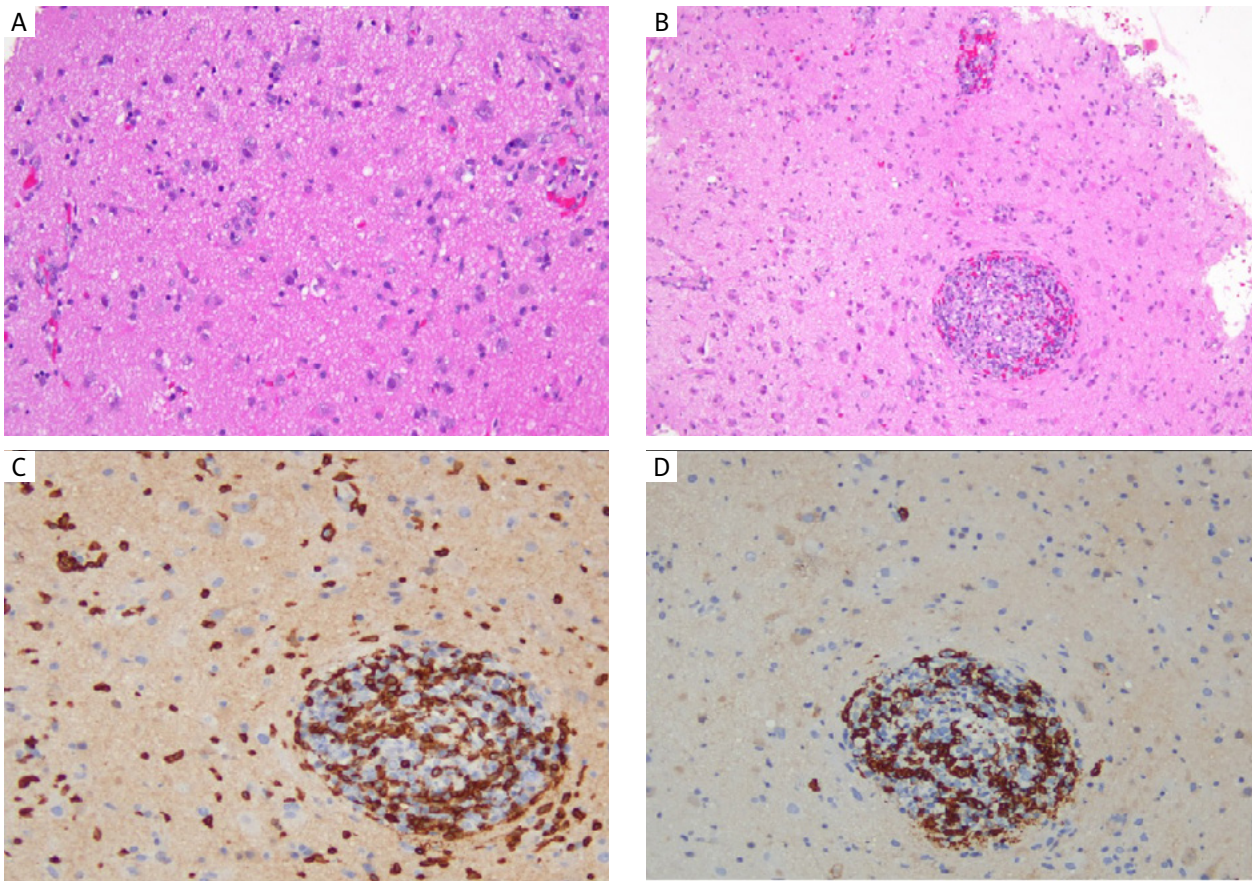

Figure 2. A) Histological examination of reactive astrocytes admixed with chronic inflammatory cells (H&E × 200). **B**) Lymphocytic rimming of blood vessels akin to brain lymphoma (H&E x 100). Immunohistochemistry revealing a mixture of reactive T lymphocytes: CD3 stain × 200 and B lymphocytes (**C**), CD20 stain × 200 (**D**)

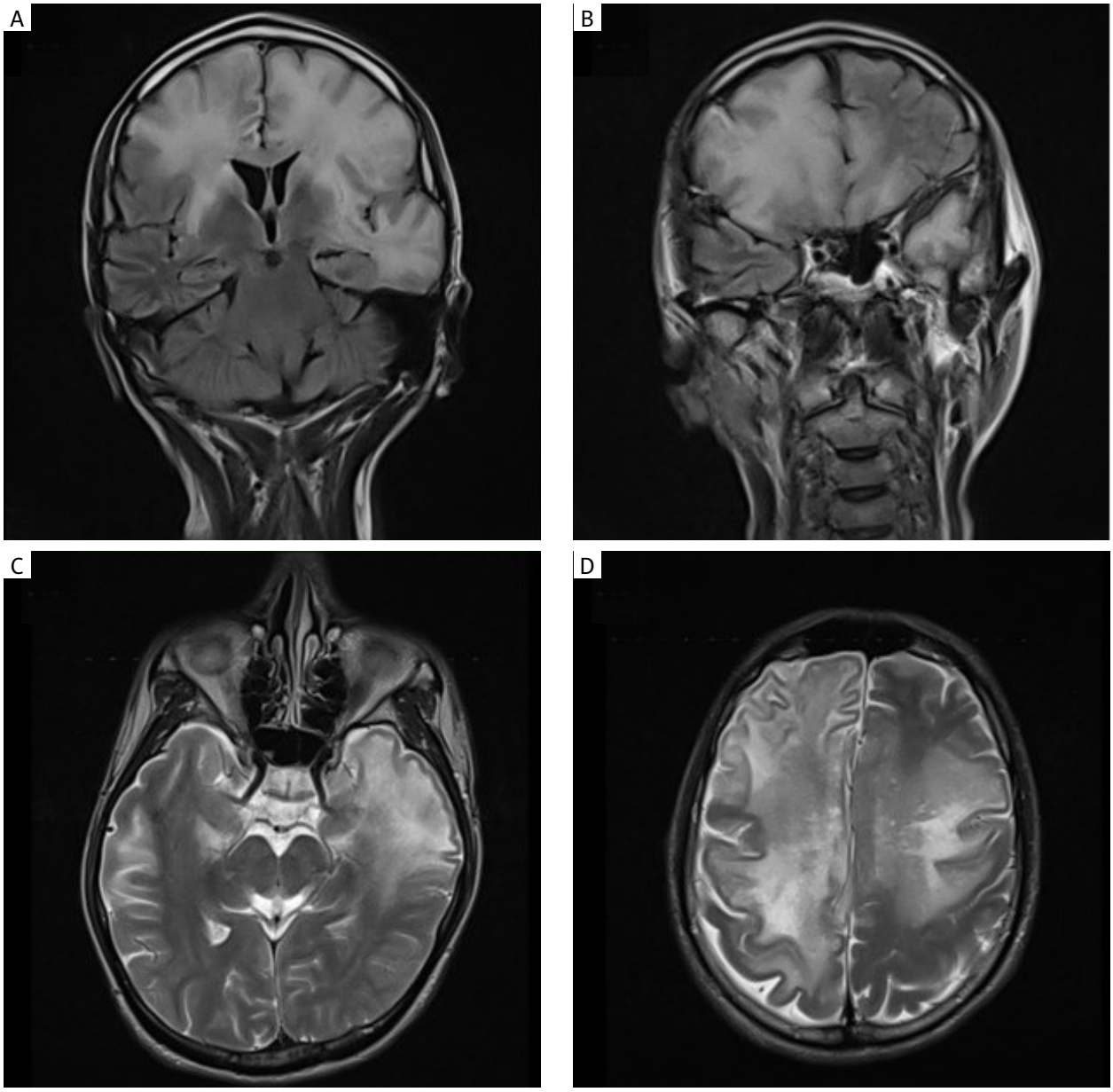

Figure 3. T2-weighted image of the second brain magnetic resonance imaging. There are multifocal abnormal signals with asymmetrical distribution involving sub-cortical, deep, and periventricular cerebral white matter as well as both frontoparietal lobes and left temporal lobe. White matter changes are confluently seen in this study. They demonstrate low signal on T1, high signal on T2, and mixed low to high signal on FLAIR, which are characteristic features of progressive multifocal leukoencephalopathy. The sulci are not effaced. There is no significant mass effect

became more dependent and weaker, confined to bed most of the time; he talked irrelevantly with constant anger and was verbally abusive. There was no hallucination or delusion observed. On neurology assessment, he was confused, the left upper limb power worsened to 1/5 from 3/5 with hypertonia and spasticity. Power of other limbs were 3/5 with hyperreflexia but sensation was intact. Cranial nerves and cerebellar assessment were normal. His CD4 count was very low at 18 cells/mm^3, while viral load was very high at 608 k copies/ml.

A second MRI revealed a significantly increased distribution of the previous lesion involving the sub-cortical and deep cerebral white matter with asymmetrical distribution compared with the first MRI scan. The signal was visualized at both frontoparietal lobes, left temporal lobe, and periventricular area. White matter changes were more confluent in the current MRI, with low signal on T1, high signal on T2, and mixed low to high signal on FLAIR (Figure 3). These findings were highly suggestive of PML. The patient was finally diagnosed with PML after four months from his first

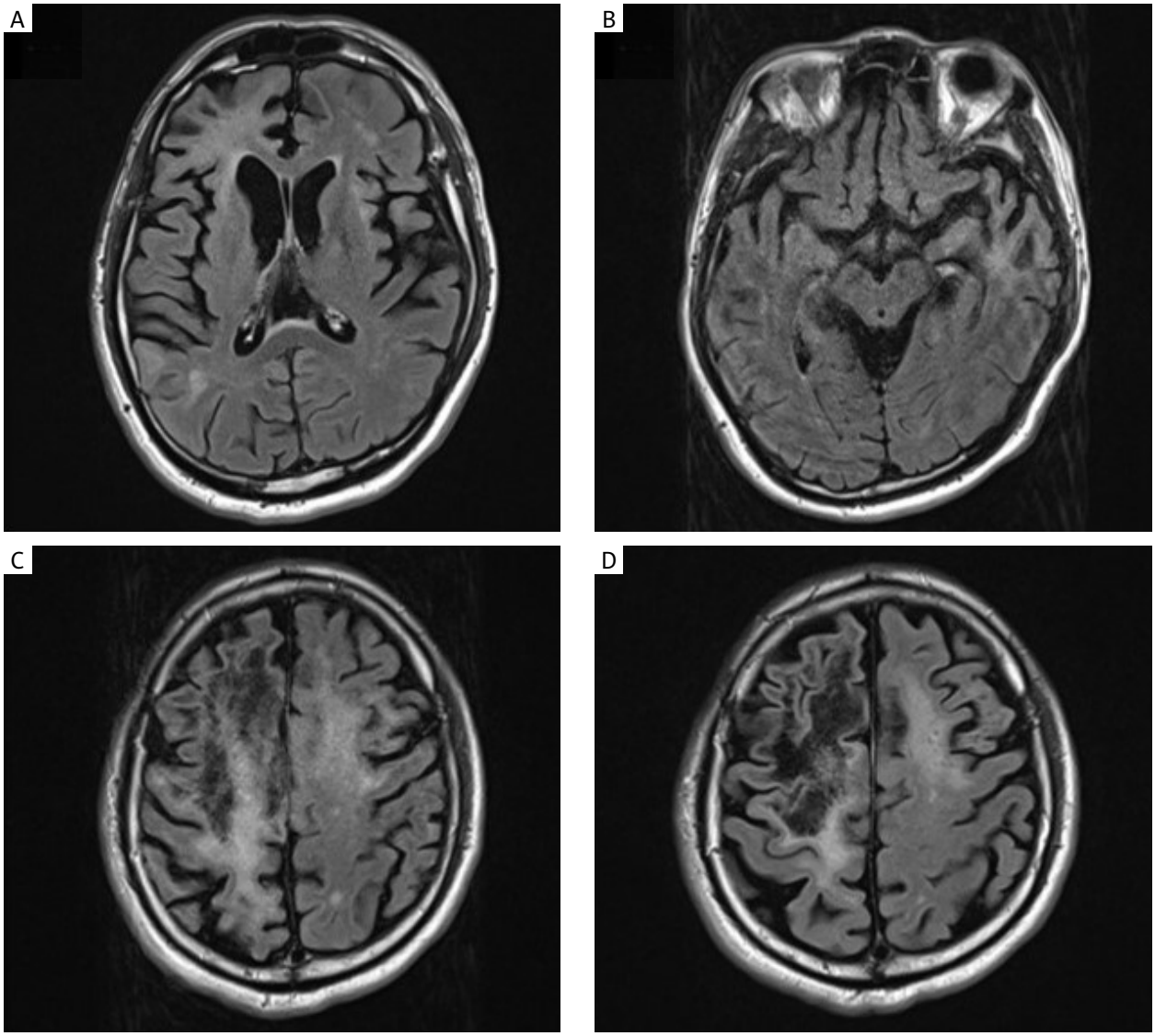

Figure 4. T2-weighted image of the third brain magnetic resonance imaging at 12 months after diagnosis. Previous multifocal abnormal signal involving sub-cortical, deep, and periventricular cerebral white matter with asymmetrical distribution are markedly reduced with associated ex-vacuo dilatation, with encephalomalacia and gliosis

presentation that was made solely based on MRI findings, as CSF test for JC virus PCR was not done due to unavailability in our center. Since there is no reliable treatment available for PML, he continued with antiretroviral therapy (ART) regime, consisting of tenofovir + emricitabine + stocrin, and intensive rehabilitation. The patient was started on desvenlafaxine and praliperidone due to personality changes.

The patient's condition slowly improved over the years with adherence to ART and consistent physiotherapy, and his latest CD4 count increased to 614 cells/ mm^3 with undetectable viral load by November 2019. A third MRI showed multifocal abnormal signal involving the sub-cortical, deep, and periventricular cerebral white matter with asymmetrical distribution markedly reduced (Figure 4). The brain was also less edematous with no more effacement of sulci. Currently, the patient is independent in activities of daily living (ADL), despite some weakness and spasticity of his left upper limb. He is able to feed himself, bathe, and ambulate independently. His cognitive function remained affected with poor judgement and memory. The patient no longer exhibits any aggressive behavior. He is still alive but remains home-confined.

Discussion

PML is a rare disease and often underdiagnosed among immunocompromised individuals [7]. Due to HIV infection, AIDS, or lymphoma, it can also affect individuals on immunomodulators, such as rituximab. PML remains under investigated both from diagnostic and therapeutic point

of view, due to its rare presentation [8]. The prevalence of PML is approximately 1 in 200,000 in the United States and Europe [6]. However, the incidence is higher among patients with HIV as compared with other immunocompromised states, for example hematological malignancy and those on immunosuppressive agents [9]. Our case showed that HIV- and JCV-associated PML may occur long before diagnosis due to atypical presentations.

The classical type of PML manifests as sub-acute neurological deficit, while the inflammatory PML is often associated with immune reconstitution inflammatory syndrome (IRIS). Our case represents the classical type of PML, who presented with two episodes of generalized tonic-clonic seizures, followed by progressive change in behavior and impaired cognitive function. Impaired cognitive function was commonly seen in classical type of PML that accounts for 45% of the population in the United States and Europe [1, 10]. Meanwhile, seizures and change in behavior are the atypical presentations, in which seizures occur in about less than a fifth of patients, often with lesions adjacent to the cortex [2, 4], and changes in behaviors account for less than 3% of PML cases [4]. Our patient developed focal hemiparesis that is the classic presentation of classical PML only four months later, leading to PML diagnosis from his second MRI findings.

In Malaysia, in view of rare PML incidence, cases with such similar presentations are often investigated with more common brain infections associated with HIV, including herpes simplex virus (HSV), tuberculous meningitis, cryptococcal meningitis, and cerebral toxoplasmosis [11]. In diagnosing PML, JCV PCR test is the diagnostic tool [12]. It can be detected early even before PML features of brain pathology are seen on MRI [12-15] due to high positive predictive value (PPV) of 92.3% in moderate to high PCR as well as high sensitivity value of > 95% [16, 17]. However, this test is not available in our facility, possibly due to being a country with low burden of HIV and AIDS [13, 14]. JCV PCR test can be beneficial in assisting clinician to diagnose PML sooner, hence it is highly recommended to be available in medical facilities.

Symptoms manifestation in PML are closely related to pathology lesions found in the brain [5]. The second brain MRI of our patient showed diagnostic features of PML, which were solitary avid and homogeneously enhanced lesions with white matter changes, particularly around the periventricular, sub-cortical, and frontoparietal area [7]. These sites of PML involvement explained bizarre symptoms in the initial presentation, which included personality changes and impaired cognitive function, often seen in frontal lobe pathology [5, 10, 16]. Even though brain biopsy assessment of this patient was inconclusive, and CSF for JC virus polymerase chain reaction (PCR) was unavailable, the brain MRI is still considered the best non-invasive method of diagnosing PML [1].

It is known that the prognosis of PML is serious, and median survival from the onset of first symptoms is 3.5-5.5 months. There are only few reports of cases with HIV-associated PML surviving more than 1.5 years [5, 18]. Various studies proved that ART treatment significantly improve survival among HIV-positive patients with PML [18, 19]. In addition, higher CD4 cell counts (> 100 cells/mm^3) at diagnosis as well as younger age have been associated with prolonged survival in other studies [5, 18]. However, surprisingly in our patient, despite having very low CD4 cell count at diagnosis, he continues to survive and improved markedly after six years from diagnosis. Even though his left upper limb weakness is still present with spasticity, the patient remains independent in his activities of daily living (ADL). This could be due to consistent adherence to ART that has been proved beneficial in many studies [18].

Conclusions

A high suspicion of PML in HIV patients presenting with bizarre neurological symptoms should be made early. We also conclude that although typical MRI features of asymmetrical white matter changes may represent other CNS pathology, JCV PCR test should be considered and made available to assist clinician to diagnose PML sooner [13, 14], especially in patients with HIV and AIDS.

Our case is the first ever reported case on PML with HIV, who survived six years after diagnosis. The prognosis shown by our patient is much better compared with other reported cases of PML with HIV [3, 19, 20]. This case illustrates that survival is possible with good compliance with ART and intensive rehabilitation. Therefore, all patients diagnosed with PML and HIV should be offered optimal antiretroviral combination therapy and appropriate supportive rehabilitation for longer survival and improvement in their ADLs.

Conflict of interest

The authors declare no conflict of interest.

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