American Journal of Psychiatry and Neuroscience
2021; 9(1): 15-18
http://www.sciencepublishinggroup.com/j/ajpn
doi: 10.11648/j.ajpn.20210901.13
ISSN: 2330-4243 (Print); ISSN: 2330-426X (Online)

Case Report

An Unusual Case of Progressive Multifocal Leukoencephalopathy in an Immunocompetent Patient Masquerading as a Stroke

Nisahan Balasingam[1], Zhi Yang Siow[1], Athula Kosgallana[2, *], Tom Robertson[3]

[1]Department of Medicine, Hervey Bay Hospital, Queensland, Australia

[2]Department of Medicine, Goulburn Hospital, New South Wales, Australia

[3]Royal Brisbane & Women's Hospital, University of Queensland, Queensland, Australia

Email address:

nisahan2004@yahoo.com (N. Balasingam), Zyang_31@yahoo.com (Z. Y. Siow), athulakosgallana@gmail.com (A. Kosgallana), thomas.robertson@health.qld.gov.au (T. Robertson)

[*]Corresponding author

To cite this article:

Nisahan Balasingam, Zhi Yang Siow, Athula Kosgallana, Tom Robertson. An Unusual Case of Progressive Multifocal Leukoencephalopathy in an Immunocompetent Patient Masquerading as a Stroke. *American Journal of Psychiatry and Neuroscience*. Vol. 9, No. 1, 2021, pp. 15-18. doi: 10.11648/j.ajpn.20210901.13

Received: February 17, 2021; **Accepted**: March 4, 2021; **Published**: March 22, 2021

Abstract: Background: Progressive multifocal leukoencephalopathy is a fatal demyelinating condition due to reactivation of latent JC virus in cerebral white matter. Its prevalence is 1in 200,000 and extremely rare in immunocompetent individuals. It can mimic subacute stroke, brain tumours and other demyelinating conditions which have different outcomes. PML typically occurs in an immunocompromised patient, where the archetype JC virus gains pathogenic potential and initiate oligodendroglial inflammation. Currently, the immune reconstitution is considered as the treatment of choice; however, paradoxical worsening with IRIS PML is a significant challenge. There is limited evidence available on how to manage PML in immune competent patients. Direct antiviral agents have no convincing evidence to-date. There is anecdotal evidence that IL-2, filgrastim, and vaccination may be helpful. Case presentation: A 74-year-old man presented with right-sided weakness and dysphasia. He was initially managed as having subacute stroke based on imaging and clinical findings. He subsequently deteriorated, triggering to revisit of the original diagnosis and repeat imaging. He underwent extensive workup, including lumbar puncture and JC viral testing. He was commenced on Mirtazapine to prevent JC viral spread; however, he later passed away. A subsequent post-mortem brain biopsy confirmed the progressive leukoencephalopathy. Conclusion: Even though extremely rare, progressive multifocal leukoencephalopathy should be considered in the differential diagnosis of progressive neurological conditions. It is essential to rule out other treatable conditions as progressive multifocal leukoencephalopathy has a fatal outcome invariably.

Keywords: Progressive Multifocal Leukoencephalopathy, JC Virus, Immunocompetent

1. Introduction

Progressive Multifocal Leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system due to reactivation of polyomavirus called John Cunningham (JCV) virus [1]. Even though PML was described early as 1952 by Ästro¨m and colleagues, the actual causative agent was identified as the JCV in a Hodgkin disease patient's brain in 1972 [2]. It causes lytic infection of oligodendrocytes. Typical clinical findings of PML are similar to a stroke, but PML is usually progressive and fatal. Almost always, PML occurs in immunocompromised patients. PML occurs in an immunocompetent patient is extremely rare [3].

2. Case Presentation

A 74-year-old gentleman presented with a history of fall to the emergency department. He presented with a history of

progressive right-sided weakness and worsening expressive dysphasia. He did not have any fever, chronic headache, visual disturbances, delirium or seizures. Even though he had hypertension, he did not take any medications for a couple of years, and his blood pressure was well controlled. He is a retired furniture mover. He is a non-smoker and took alcohol occasionally. He did not use illicit drugs. On examination, he had an average body built and oriented to time, place and person. He was hemodynamically stable without any abnormal pulse or murmur. His respiratory and abdominal examinations were unremarkable. Nervous system examination revealed expressive dysphasia. Cranial nerves and cerebellar examinations were normal. Motor examination showed right side MRC scale four weaknesses with marginally increased tone and reduced sensation. Reflexes were equal bilaterally, and plantar reflexes showed a withdrawal response.

His blood investigations include complete blood count, renal functions, and electrolytes, did not show any significant abnormality. Serum Alanine Transaminase was 115U/L, Aspartate transaminase was 115U/L, Alkaline phosphatase was 340 U/L, and gamma-glutamyl transferase was 370U/L. His total serum bilirubin was 34micromol/L, with conjugated bilirubin was 14micromol/L. He had head Computed tomography (CT) and Magnetic Resonance Imaging (MRI), which showed a large volume established infarct in the left centrum semiovale in keeping with early infarction changes.

He was managed as an acute stroke with antiplatelet medications and rehabilitated for a month. But he continued to deteriorate in terms of weakness and dysphasia. Interval MRI showed a left frontoparietal lesion with an early transcallosal spread to the right frontal lobe. Neurological, neurosurgical and neuro-radiological input sought, and lumbar puncture performed to confirm possible PML. JC virus was detected in cerebrospinal fluid (CSF) as well as in blood. He was extensively investigated for immunosuppression. IgG, IgA, IgM were elevated (23g/L, 7g/L, 2.8g/L, respectively) with elevated kappa and lambda chains (69mg/L and 56mg/L); however, the ratio was normal. His initial lymphocytes count was 1320/mm3, but later it reduced to 580/mm3 with CD3 (T cells) were 61%, helper T-cells 30%, cytotoxic T cells 31%. Total B cells were 18%, and NK cells were 21%. A hematological opinion was sought, and lymphopenia was considered reactive. His Anti-nuclear antibody was homogenous 640 but double standard DNA, retroviral studies (repeatedly done), hepatitis B, C status, ANCA, Extractable nuclear antigen, rheumatoid factor, Treponema pallidum Hemagglutination Assay, serum protein electrophoresis, urine Bence Jones proteins, Human T cell lymphotropic viral studies were negative. Serum angiotensin-converting enzyme level was not elevated. Tumor markers were negative, except CA 19.9 was 120kU/L (Normal value <35kU/L). His ultrasound abdomen showed an atrophic pancreas, and MRCP (magnetic resonance cholangiopancreatography) did not reveal any lesions in the pancreas.

He was managed with Mirtazapine with palliative intent. Unfortunately, he passed away two months after the diagnosis. Autopsy arranged to confirm PML with his and his family with prior consent.

Autopsy examination of the brain revealed multifocal areas of degeneration of the white matter, with the largest site being present in the left hemisphere's centrum semiovale. Areas of degeneration were associated with softening and grey discoloration of the white matter with a granular texture to the cut surface. Histologic examination revealed demyelination associated with oligodendroglia, showing the typical amphophilic 'ground-glass' intranuclear viral inclusions (see figure 1). There were associated reactive astrocytes, including large, bizarre forms specific to PML (see figure 2). Lesions were widespread throughout the cerebrum, brainstem and cerebellum. Nucleic acid amplification on autopsy brain tissue confirmed the JC virus's presence and coincidentally, human herpesvirus 6 (HHV6).

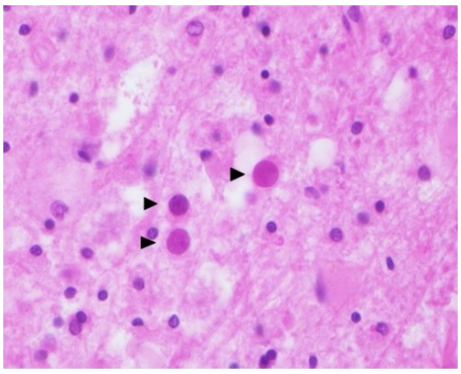

Figure 1. *Cowdry B like viral inclusion in Oligodendrocytes.*

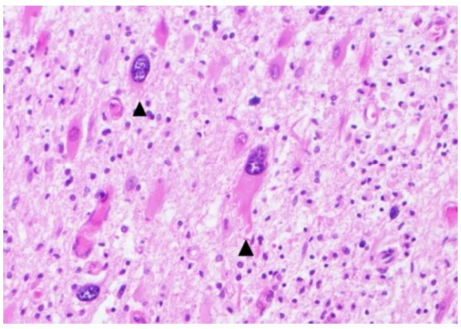

Figure 2. *Foamy macrophages.*

3. Discussion

JCV is prevalent in 50-90% of healthy adults, and around 85%of the population has antibodies to the JC virus. JCV is an ancient virus co-evolved with humans, and primary infection happens in early childhood via person to person, typically through parents. Once primary infection occurs, the JC virus remains latent in the kidney and lymphoid organs [4, 5]. It usually reactivates when there is profound cellular immune suppression. The dormant archetype JCV acquires pathogenic potential via NCCR genetic rearrangement and becomes a prototype, a neuropathogenic variant responsible for PML [6]. It is still unclear whether the dormant JCV in the brain causes the PML or circulating CD34 B cells containing prototype JCV causes PML [7]. JCV binds to both serotonergic 5-HT_{2A}

and N-linked glycoprotein, enabling its cellular entry [8].

PML is well reported in association with immuno-compromised diseases like AIDS, hematological malignancies, organ transplant recipients and patients using newer immunomodulating agents like natalizumab and rituximab [9, 10, 11]. PML also reported in the immune reconstitution setting as IRIS PML in HART treatment in HIV patients and with Natalizumab in MS patients [12, 13]. There are only a few case reports of PML patients without definitive immunosuppression in the literature [3, 14].

The demyelination, which is the cardinal feature of PML, is typically a multifocal process. The white matter of the brain is affected, and usually, lesions are one millimeter to several centimeters in size. The typical histological findings in PML are multifocal demyelination, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei and hyperchromatic enlarged oligodendroglial nuclei [15, 16].

Clinically PML might present with motor weakness, gait abnormality, incoordination, visual field problems, language disturbances, behavioral, cognitive problem or seizure. PML never involves the peripheral nervous system. Our patient presented with motor weakness and speech abnormality.

The characteristic CT appearance of PML is white matter hypodense lesions without mass effect and rarely contrast enhancement. But MRI of the brain is more sensitive than CT studies. MRI shows hyperintense lesions on T2-weighted fluid-attenuated inversion recovery (FLAIR) images in the affected regions. [17]. The JC virus's demonstration by PCR in CSF is highly sensitive and specific for PML [8]. Diagnosis of PML is not straightforward because multiple sclerosis, central nervous system vasculitis, brain malignancy, varicella-zoster leukoencephalitis, acute disseminated encephalomyelitis and posterior reversible encephalopathy (PRES) may mimic clinically and radiographically. Also, JC virus viremia can occur in healthy people, and CSF contamination might result in positive CSF results. A negative PCR in CSF does not rule out PML. Therefore, CSF finding with appropriate clinical and imaging features needs to be present to diagnose PML. Brain biopsy is required to confirm the diagnosis [18]. Our patient fulfilled all the features, including the autopsy features.

There is limited data on direct viral suppression or limiting viral spreading with current medications. These includes, cytarabine [19], cidofovir [20], mefloquine [21], topotecan [22] and mirtazapine [23]. The most widely used strategy now is immune reconstitution. There are anecdotal reports on the use of IL-2 [24], Filgrastim [25] and active vaccination [26]. The most recent trails looked at the use of immune checkpoint, which targets programmed cell death protein 1 (PD1) inhibitors which had promising results [27].

HHV-6 is a ubiquitous herpes virus responsible for roseola in young children. The virus is neurotropic and can be reactivated with immune suppression and causes encephalitis. The involvement of HHV-6 in the demyelination process of PML with the JC virus as a co-agent remains unclear [28-30].

Unusually, our patient did not show any evidence of immunosuppression, even with extensive investigations. But it might be possible that transient immunosuppression might have played a role in the virus's reactivation in our patient. This case illustrates the importance of considering rare diseases with atypical features when there is a diagnostic challenge.

4. Conclusion

PML is often an under-diagnosed or misdiagnosed neurological condition which has a fatal outcome. It can mimic many other neurological conditions clinically and radiologically. A high index of suspicions and awareness of this rare condition is critical in inpatient care in terms of mortality, morbidity and medico-legal perspective. Diagnosis of PML is based on MRI and CSF JC viral detection; however, definitive diagnosis needs brain biopsy and post-mortem studies. Once confirmed, the diagnosis, the medical management with immune reconstitution is the most effective therapeutic option. Unfortunately, immune reconstitution has the potential drawback of inducing paradoxical IRIS PML. There is some evidence that mirtazapine, a commonly used antidepressant, may reduce the local viral spread. The recent work on checkpoint inhibitors and adoptive immunotherapy will bring therapeutic agents in future [31].

Abbreviations

PML: progressive multifocal leukoencephalopathy; JC virus: John Cunningham virus; HHV6: human herpesvirus 6

References

[1] Padgett BL, Walker DL, ZuRhein GM, Eckroade EJ, Dessel BH. Cultivation of papova-like virus from the human brain with progressive multifocal leukoencephalopathy. *The Lancet*. 1971; vol. 1, no. 7712, 1257–1260.

[2] Astrom KE, Mancall EL, Richardson EP. Progressive multifocal leuko-encephalopathy, a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain*. 1958; vol. 81, no. 1, 93–111.

[3] Gourineni VC, Juvet T, Kumar Y et al. Progressive multifocal leukoencephalopathy in a 62-year-old immunocompetent woman. Case reports in neurological medicine, 2014.

[4] Moens, U. et al. Biology, evolution, and medical importance of polyomaviruses: an update. *Infect. Genet. Evol. 2017;* 54, 18–38.

[5] Zheng, H.-Y, Kitamura, T, Takasaka, T, Chen, Q. & Yogo, Y. Unambiguous identification of JC polyomavirus strains transmitted from parents to children. *Arch. Virol. 2004;* 149, 261–273.

[6] Pavlovic D, Patel M. A, Patera A. C. & Peterson I. Progressive Multifocal Leukoencephalopathy Consortium. T cell deficiencies as a common risk factor for drug associated progressive multifocal leukoencephalopathy. *Immunobiology. 2018;* 223, 508–517.

[7] Wollebo, H. S, White M. K, Gordon J, Berger J. R. & Khalili, K. Persistence and pathogenesis of the neurotropic polyomavirus JC. *Ann. Neurol. 2015;* 77, 560–570.

[8] Brew BJ, Davies NWS, Cinque P, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nature Reviews Neurology*. 2010; vol. 6, no. 12, 667–679.

[9] Wijburg, M. T. et al. Performance of PML diagnostic criteria in natalizumab-associated PML: data from the Dutch-Belgian cohort. *J. Neurol. Neurosurg. Psychiatry. 2019;* 90, 44–46.

[10] Bellizzi A, Nardis C, E, Anzivino et al. "Human polyomavirus JC reactivation and pathogenetic mechanisms of progressive multifocal leukoencephalopathy and cancer in the era of monoclonal antibody therapies," *Journal of Neurovirology*. 2012; vol. 18, no. 1, pp. 1–11.

[11] Carson KR, Focosi D, Major EO et al. "Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efal- izumab: a review from the Research on Adverse Drug Events and Reports (RADAR) project," *The Lancet Oncology*. 2009; vol. 10, no. 8, pp. 816–824.

[12] Fournier A, et al. Immune reconstitution inflammatory syndrome unmasking or worsening AIDS-related progressive multifocal leukoencephalopathy: a literature review. *Front. Immunol. 2017;* 8, 577.

[13] Warnke C, et al. Cerebrospinal fluid JC virus antibody index for diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann. Neurol. 2014;* 76, 792–801.

[14] Graves B, Bambach W, Hosey Rebecca, Hosey Jonathan. Non-HIV PML: A Case of PML in an Immunocompetent Patient with a Retrospective Review on Non-HIV PML Risk Factors. Neurology. 2014; 82, P4.320.

[15] Bergui, M. et al. Progressive multifocal leukoencephalopathy: diffusion-weighted imaging and pathological correlations. *Neuroradiology. 2004;* 46, 22–25.

[16] Whiteman ML, et al. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. *Radiology. 1993;* 187, 233–240.

[17] Miyagawa, M. et al. Low signal intensity in U-fiber identified by susceptibility-weighted imaging in two cases of progressive multifocal leukoencephalopathy. *J. Neurol. Sci. 2014;* 344, 198–202.

[18] Berger J R, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013; 80, 1430–1438.

[19] Hall, C. D. et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N. Engl. J. Med. 1998;* 338, 1345–1351.

[20] De Luca, A. et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. 2008; *AIDS* 22, 1759–1767.

[21] Clifford, D. B. et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J. Neurovirol. 2013;* 19, 351–358.

[22] Royal, W. et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J. Neurovirol. 2003;* 9, 411–419.

[23] Jamilloux, Y. et al. Treatment of progressive multifocal leukoencephalopathy with mirtazapine. *Clin. Drug Investig. 2016;* 36, 783–789.

[24] Przepiorka, D. et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transpl. 1997;* 20, 983–987.

[25] Stefoski D. et al. Treatment of natalizumab-associated PML with filgrastim. Ann. Clin. Transl. Neurol. 6, 2019; 923-931.

[26] Sospedra, M. et al. Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1. *Clin. Infect. Dis. 2014;* 59, 1588–1592.

[27] Nagai H, Muto M. Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: a review and update. *Int. J. Clin. Oncol. 2018;* 23, 410–420.

[28] Mock DJ, Powers JM, Goodman AD, Blumenthal S, Ergin N, et al. Association of human herpesvirus 6 with the demyelinative lesions of progressive multifocal leukoencephalopathy. J. Neurovirol. 1999; 5: 363-373.

[29] Blumberg BM, Mock DJ, Powers JM, Ito M, Assouline JG, et al. He HHV6 paradox: ubiquitous commensal or insidious pathogen? A two-step in situ PCR approach. J Clin Virol. 2000; 16: 159-178.

[30] Yao K, Gagnon s, Akhyyani N, et al. Reactivation of Human Herpesvirus-6 in natalizumab Treated Multiple Sclerosis Patients. Plos one. 30 Apr 2008; 3 (4): e2028.

[31] Balduzzi, A. et al. Polyomavirus JC-targeted T-cell therapy for progressive multifocal leukoencephalopathy in a hematopoietic cell transplantation recipient. *Bone Marrow Transpl. 2011;* 46, 987–992.