

# A Chronic Lymphocytic Leukemia Patient with Progressive Multifocal Leukoencephalopathy Caused by John Cunningham Virus

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**ABSTRAK**

*Kasus progressive multifocal leukoencephalopathy (PML) jarang terjadi, tapi berakibat fatal yang menyebabkan gangguan neurologi yang berat. PML merupakan suatu manifestasi klinis yang biasanya berkaitan dengan infeksi virus John Cunningham (JC). PML juga berhubungan dengan kondisi keganasan, terutama keganasan hematologi, misalnya leukemia limfositik kronik. Sampai saat ini belum ada terapi yang tepat untuk PML yang diakibatkan virus JC, sehingga prognosis pada penderita ini sangat buruk.*

*Laporan kasus ini menyajikan suatu kasus yakni wanita berusia 67 tahun yang menderita LLK dengan keluhan utama kejang. Gejala klinis pasien, hasil MRI kepala serta hasil biopsi otak mendukung diagnosis PML akibat virus JC. Pasien mendapatkan terapi mefloquine 250 mg/hari, tetapi tidak mengalami perbaikan klinis.*

**Kata kunci:** *progressive multifocal leukoencephalopathy (PML), virus John Cunningham, leukemia limfositik kronik (LLK).*

**ABSTRACT**

*Progressive multifocal leukoencephalopathy (PML) is a rare but fatal disease leading to severe neurological impairments. PML is a clinical manifestation, which is usually associated with John Cunningham virus (JCV) infection. It is also correlated to malignancies that mainly include hematologic malignancies such as chronic lymphocytic leukemia (CLL). Until now, no specific treatment has been established for JCV-induced PML; therefore, the prognosis of this disease is poor.*

*We present a case of a 67-year-old woman who suffered from CLL with a chief complaint of seizure. Her clinical symptoms, results of brain MRI and biopsy were suggestive for the JCV-induced PML. The patient had received treatment using mefloquine at dose of 250 mg/day with no clinical improvement.*

**Keywords:** *progressive multifocal leukoencephalopathy (PML), John Cunningham virus, chronic lymphocytic leukemia (CLL).*

**INTRODUCTION**

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder, which is characterized by clonal proliferation and

accumulation of malignant B cell lymphocytes in the bone marrow, vascular and lymphoid tissue.<sup>1</sup> Like other malignancies, infection is still the main reason for high morbidity and mortality rate

in patients with CLL. The infection, particularly viral infection, may lead to CLL-associated immune dysfunction.<sup>2</sup>

John Cunningham Virus (JCV) belongs to the Polyomaviridae family. In 1971, the virus was first isolated from the brain tissue of a patient with Hodgkin disease.<sup>3</sup> JCV is commonly found in community and causes infection in 70-90% human population, which usually occurs in childhood and adolescence. JCV is more common in urban than rural areas since high concentration of JCV has been widely found in the sewage of different cities. Contaminated water could be potential source of JCV infection.<sup>4</sup>

JCV causes PML (Progressive Multifocal Leukoencephalopathy) and it mostly occurs in immunodeficient condition such as in patients with AIDS (Acquired Immune Deficiency Syndrome) or patients receiving immunosuppressant treatment. PML is a rare but fatal disease as it causes central nervous system disorder, which is characterized by neuron demyelination leading to severe neurologic impairment.<sup>5</sup> The disease is commonly associated with malignancy, particularly with hematological malignancies such as Hodgkin Lymphoma, Non-Hodgkin Lymphoma, CLL, myeloma, Waldenstrom Macroglobulinemia and patients undergoing hematopoietic stem cell transplantation (HSCT).<sup>6</sup> A retrospective study evaluating CLL patients from January 2000 until June 2008 found that PML incidence is approximately 11.1 per 100,000 person year.<sup>7</sup>

### CASE ILLUSTRATION

A 67-year-old female patient was admitted to our emergency department with a chief complaint of recurrent convulsion since 3 days prior to admission. She had been diagnosed with CLL since 8 years ago and had received chlorambucil for her treatment. In the previous 3 months, she complained about memory loss and right-sided weakness. She was then admitted to a hospital and diagnosed with stroke and lymphoma. She had progressive weakness in spite of the treatment that she had received. In addition to her weakness, she also had slurred speech, confusion and sleepiness.

Multiple magnetic resonance imaging (MRI)

was performed and we noted increased signal intensity in the white matter of both left and right occipital lobes, which was observed on T2-weighted MRI scan. The left side had worse condition as the increased signal intensity had been extended forwards into the left temporal lobe and downwards into left thalamus. Low signal intensity was observed on T1-weighted MRI scan and no enhancement was noted in the contrast-enhanced MRI.

Brain biopsy of the left occipital lesion was performed and it showed bizarre-shaped astrocytes, foamy macrophages, enlarged oligodendrocytes, perivascular lymphocyte aggregation. The rare macrophages were engulfed by myelin debris and the oligodendrocyte nuclei in the white matter were stained positive for polyomavirus. Based on her clinical symptoms, results of brain MRI and biopsy, a diagnosis of JCV-induced progressive multifocal leukoencephalopathy (PML) was made and the patient received mefloquine treatment at the dose of 250 mg/day. The patient was then admitted to the intensive care unit (ICU). In the ICU, she was on anti-convulsion medication and the mefloquine treatment was stopped. She never had convulsion again, but she became coma over the following one months. Then the patients came home forcibly from the hospital, and used a portable respirator for approximately 2 months, and finally the patients died at home.

### DISCUSSION

CLL occurs more common in men than women and the average age at the time of diagnosis is around 65 years with only 10-15% cases occur in patients aged less than 50 years.<sup>8</sup> Most CLL cases are asymptomatic and the diagnosis is usually made accidentally by laboratory examination.<sup>1,9,10</sup> The diagnostic criteria for CLL according to International workshop for CLL and National Cancer Institute include the increased absolute lymphocyte count of more than  $5 \times 10^9/L$  ( $5000/\mu L$ ) in peripheral blood with specific morphology and immunophenotypes. To confirm the diagnosis, a peripheral blood smear must be performed. The blood smear will then reveal lymphocytosis with a dominance of mature small lymphocytes and smudge cells. The diagnosis of CLL can

be confirmed when there are more than 30% of nucleated cells in the bone marrow aspirate.<sup>1,10</sup> Once the diagnosis of CLL has been confirmed, we should perform staging to predict prognosis and determine appropriate treatment.

Treatment should be given at symptomatic or progressive intermediate stage.<sup>10,11</sup> The first-line treatment for CLL includes a single chemotherapy using alkylating agents (chlorambucyl or cyclophosphamide). Combination chemotherapy is reserved for patients who had failed to respond to treatment using chlorambucyl or cyclophosphamide alone either with or without prednisone, which include COP (cyclophosphamide, vincristine and prednisone). While the second-line treatment includes purine analogs (fludarabine) or monoclonal antibody (rituximab or alemtuzumab).<sup>10,12</sup>

History taking of our patient reveals that she has had a diagnosis of CLL since 8 years ago and has received single chemotherapy using an alkylating agent, i.e. chlorambucil. The patient has a risk factor for infection due to her immunodeficient condition, which may be caused by either the disease itself or by the effect of chemotherapy. CLL is usually found together with immune dysfunction that may lead to multiple complications. Any defect in cell-mediated immune system including abnormal number or function of B-cell lymphocytes, T lymphocytes, Natural Killer (NK cells), neutrophils and abnormal monocytes or macrophages or defect in humoral immune response such as low titer of gamma globulin has been considered to have some roles in the development of multiple complications in patients with CLL.<sup>2,13</sup> The complications particularly affect central and peripheral nervous

systems, which are the target organ for CLL-related complications and serious consequences may occur.<sup>14</sup>

John Cuningham Virus (JCV) is a double-stranded DNA virus. It belongs to human polyomavirus family, which is also known as papovavirus. The virus genetically resembles BKvirus and SV40. It was first identified using electron microscope in 1965 by Zurhein and Chou and subsequently cultured by Silverman and Rubinstein. The virus was named after the first patient who was diagnosed with PML.<sup>7,15</sup> Epidemiological studies show that JCV affects approximately 75-80% human population and half of the infection cases occur during childhood. Primary infection is usually asymptomatic and 85% of adult population usually have antibody against JCV. The virus infiltrates human body through inhalation or oral route from water contaminated with urine or fecal material from infected individual. After the infiltration, JCV will develop local infiltration in tonsillar stromal cells and lymphocytes or in the upper and lower gastrointestinal tract, which may serve as the initial site of viral infection. Viral replication then takes place in tonsillar and intestinal lymphoid tissue. It may become a latent infection and being dormant in some of body parts such as tonsil, kidney, lymphoid tissue, and bone marrow.<sup>16-19</sup> Reactivation of latent infection usually occurs in kidney and brain tissue.<sup>19</sup>

Cellular immune response has a role of defense mechanism against JCV infection. CD4 T-helper cells recognize virus particle and stimulate CD8 T-cytotoxic cells to eliminate the virus. In patients with CLL, there are changes of gene expression in T cells. In CLL patients there was a change in gene expression in T

**Table 1.** Staging system according to Rai and Binet for CLL<sup>1</sup>

	Binet stages			Rai stages	Median survival
Low risk	A	Hb $\geq$ 10, platelets $\geq$ 100 000, $\leq$ 2 sites involved	0	Lymphocytosis in blood and bone marrow	> 10years
Intermediate risk	B	Hb $\geq$ 10, platelets $\geq$ 100 000, $\geq$ 3 sites involved	I	Lymphocytosis + lymphadenopathy	5-7 years
			II	Lymphocytosis + splenomegaly and/or hepatomegaly	
High risk	C	Hb < 10, or platelets < 100 000	III	Lymphocytosis + Hb <11.0	< 3-4 years
			IV	Lymphocytosis + platelets < 100 000	

lymphocyte. In particular, there is a failure in CD4 as well as CD8 T cell differentiation into Th1 subsets; therefore, the patients are more susceptible to have viral infection.<sup>6</sup> In addition, the B cells of patients with CLL also TGF- $\beta$ , which has an immunosuppressive role that can cause blocking of lymphocyte proliferation and activation as well as blocking of macrophage activation.<sup>9</sup>

Severe T-cell (cellular) immune deficiency is associated with reactivation of JCV. Suppressed cellular immune response due to HIV infection is the main reason of JCV reactivation and it occurs in 80% of patients with PML. It also can occur in patients with hematologic malignancy (14%), with transplantation (5%) or patients with autoimmune disease who receive immunomodulator therapy (3%).

Epidemiological studies have demonstrated that PML is a clinical manifestation, which is often associated with JCV infection.<sup>3</sup> PML or progressive multifocal leukoencephalopathy is a neurologic abnormality characterized by myelin damage or demyelination of the central nervous system, which is induced by JCV. PML has a slow progression and it gets worse leading to severe brain damage resulting in death within 4 to 6 months; while sometimes, it may remain stagnant.

Leukoencephalopathy in PML abbreviation indicates that it generally attacks brain, particularly the subcortical white matter and mostly affects parietal and occipital lobes; however, in some cases, it may also attack the gray matter.

Although demyelination can occur in every part of the white matter, but it also can occur in the brain stem and cerebellum. In general, it is a multifocal process.<sup>5,7</sup> Visual defect is a common symptom and it can be found in approximately 35 to 45% cases. Cognitive impairment including unstable emotion, memory loss and dementia may occur in one third of cases. Motor weakness can be found in 25 to 33% cases and other symptoms may also appear including speech difficulty and convulsion.<sup>5,7,20</sup> PML has a wide variation of clinical presentation, which can be difficult to diagnose or to differentiate it with other diseases such as ischemic brain disease, vasculitis, brain

neoplasma (glioma or lymphoma), central nervous system infection (HIV encephalopathy, herpes simplex encephalopathy, neurosyphilis).<sup>21</sup> In our patient, we found several symptoms including right-sided hemiparesis, speech problem, sleepiness and confusion. Later, the patient had multiple recurrent seizures and was diagnosed with stroke and brain lymphoma. However, no improvement was seen although she was on treatment and her condition worsened with poor prognosis. Her laboratory work-up showed the following results: non-reactive syphilis TP antibody test, non-reactive anti HIV test, non-reactive IgM and IgG toxoplasma, which suggest that infection of central nervous system could be excluded.

The association between JCV infection and PML was first reported by Padgett et al in 1971. JCV was isolated from a PML patient in a postmortem examination.<sup>22</sup> JCV can be found in B cell lymphocytes from the peripheral circulation (hematogenous infiltration) and it may further infiltrate the central nervous system by penetrating blood brain barrier. The lymphocytes later eject virion and infect oligodendrocytes as well as astrocytes. The mechanism possibly occurs through 5-HT<sub>2A</sub> serotonin receptor.<sup>23,24</sup> Oligodendrocyte is a myelin producing cell in the central nervous system and it is the main target of JCV infection. JCV can also attack astrocytes, which causes astrocytes to swell, to have lobulated nuclei and to take bizarre shape, which is similar to nuclear structure.<sup>5</sup> PML case was first reported in patients with CLL and Hodgkin disease in 1958.<sup>3</sup> Although PML usually occur in patients with HIV, but 15% cases occur in individuals with lymphoproliferative disorders (LPDs) including patients with CLL, CML, and Hodgkin disease. Before 1989, LPDs-associated PML was reported mainly in patients with Hodgkin disease (63%) who receive alkylating agents therapy (monotherapy or combination therapy) and/or radiation. Since 1989, LPDs-associated PML more likely occurs in patients with CLL (46%) than those with Hodgkin disease (25%). Later, the paradigm of treatment for CLL and other lymphoproliferative disease was shifted to purine analogs and rituximab.<sup>22</sup> Over the last decades,

the standard regimen for CLL treatment includes chlorambucil, an alkylating agent, which is usually given as a monotherapy or a combination therapy with steroids.<sup>2</sup> When using the treatment, most patients usually experiences bacterial infection such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and gram-negative bacteria in the intestine. It is also associated with infection due to mucosal bacteria such as airway tract infection and the infection is usually recurrent. The conventional alkylator-based therapies is rarely associated with fungal or viral infection.<sup>2</sup> The risk factor of having infection in our patient may be due to the following reason, i.e. she was a patient with CLL, which means that she had immunocompromised status since she also received immunosuppressant therapy (chlorambucil). Moreover, she had a history of using corticosteroid treatment, which put her into a higher risk for infection. When she received treatment using alkylating agent (chlorambucil), she suffered from diarrhea, recurrent respiratory tract infection, Herpes Zoster infection and ultimately, JCV infection.

The diagnosis of PML was made based on clinical manifestations, laboratory findings and results of radiological examination as well as histopathological examination. Radiological examination has an important role in diagnosis and in the follow up of JCV infection. Magnetic resonance imaging (MRI) may demonstrate multifocal lesions without any contrast enhancement or mass effect. Hypointense signal can be found in T1-weighted MRI scan; while hyperintense signal may be prominent in

the T2-weighted MRI scan when the results are compared to the images of normal white matter. The lesion is particularly predominant in the white matter of periventricular, subcortical frontal and parieto-occipital areas. The distribution of lesion is usually asymmetric, diffuse, subcortical and it is localized in the white matter. The CT scan may reveal focal or multifocal lesion without any enhancement or mass effect.<sup>3,7,25</sup>

The MRI of our patient revealed a hyperintense signal in the white matter of both left and right occipital lobes, which was observed on T2-weighted MRI scan. The signal was more intense in the left side hemisphere and the intensity extended to anterior into left temporal lobe and left thalamus; while hypointense signal was found in T1-weighted MRI scan and the non-absorbed contrast lesion, which characterized the signs of PML. The course of the disease later showed that the lesion extended to brain stem (**Figure 1**).

Detection of JCV DNA by PCR can be performed using specimens from cerebrospinal fluid (CSF) or brain biopsy. PCR using CSF specimen has 74% to 93% sensitivity and 92% to 99% specificity; while when using brain biopsy, the test has 64% to 96% sensitivity and 100% specificity.<sup>7</sup> The risk of complication is 2.9% and the morbidity rate is 8.4%. Stereotactic brain biopsy is a standard diagnostic procedure for PML.

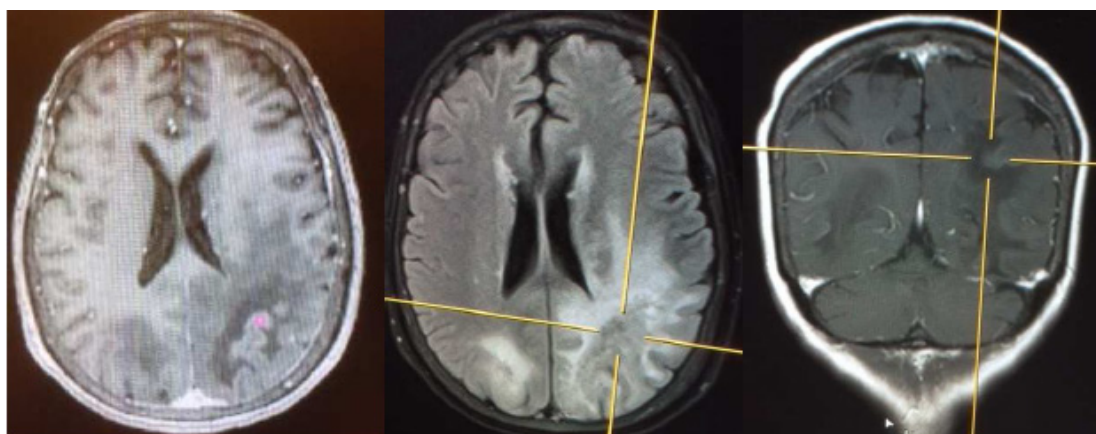
On histopathological examination, we can observe single or multiple demyelination area containing JCV-infected oligodendrocytes with enormous nuclei found at the periphery of



**Figure 1.** Results of imaging in a patient with PML

**Table 2.** Diagnostic criteria for PML<sup>3</sup>

Diagnosis	Clinical features	Imaging features	JCV DNA in CSF	Typical Histopathological Features with a Demonstration of JCV DNA
Definite PML	+	+	+	-
Definite PML	+	+	-	+
Presumptive PML	+	+	-	-

**Figure 2.** MRI-guided stereotactic brain biopsy for left occipital lobe lesion

the lesion and reactive gliosis, bizarre-shaped astrocytes, lipid-laden macrophages, which phagocyte myelin, and cellular debris.<sup>3,7</sup> The JC virus genome and protein expression can be detected using in situ hybridization and immunohistochemistry.<sup>26</sup>

In our patient, we performed a MRI-guided stereotactic brain biopsy for her left occipital lobe lesion (**Figure 2**). The biopsy revealed bizarre-shaped astrocytes, foamy macrophages, enlarged oligodendrocytes, aggregation of perivascular lymphocytes, rare macrophages with engulfed myelin debris. The oligodendrocytes in the white matter were stained positive for polyomavirus, which indicates that the patient was reactive to JCV test. The test was performed in Canada; therefore, based on her clinical signs and symptoms as well as the results of imaging and histopathological examination, the patient was diagnosed with definite PML.

There was no specific treatment for JCV infection. The main approach of our strategy was to restore the patient's adaptive immune system as it may improve her survival.<sup>26</sup> In HIV-negative patients, immunosuppressant treatment is usually

stopped. There are several specific regimens for eliminating JCV, which include cytarabine, cidofovir and topotecan, which have been used in some clinical trials; however, no clinical advantage has been demonstrated. Moreover, some toxicities and side effects of the treatment should be carefully considered.<sup>3</sup> Treatment using 5-HT<sub>2a</sub> serotonin receptor antagonists (risperidone and mirtazapine), which block infection of glial cells by JCV may be useful for treating PML; however, further studies should be conducted to provide sufficient evidences.<sup>27,28</sup> In June 2010, a study first reported that a PML patient had a successful treatment using mefloquine. Mefloquine is an anti malaria drug that works against JCV infection. The drug can probably eliminate virus and thus prevent further neurological damage; however, recent studies have not demonstrated any significant result.<sup>29,30</sup>

After our patient had been diagnosed with PML, the immunosuppressant medication including chlorambucil was stopped so that the patient could have a recovery of her immune system. Moreover, mefloquine was given to overcome her JCV infection; however, no

clinical improvement was seen. The mortality rate of LPDs-associated PML mortality rate is more than 90%.<sup>22</sup> The disease has a rapid clinical progression and when it is not treated immediately, the median overall survival is approximately 3.5 month.<sup>31</sup> Until now there is no specific treatment available for JCV-induced PML; therefore, the prognosis is poor.<sup>7</sup> The clinical condition of our patient got worse and thus her prognosis was also bad.

## CONCLUSION

Progressive multifocal leukoencephalopathy (PML) is a neurologic abnormality, which is characterized by myelin damage (demyelination) of the central nervous system and it is associated with JCV infection. Our main strategy was to restore the patient's adaptive immune system. Until now there is no specific treatment for JCV-induced PML; therefore, the prognosis of the disease is poor.

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