Progressive Multifocal Leukoencephalopathy in a 62-Year-Old Immunocompetent Woman

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Case Report

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Progressive multifocal encephalopathy (PML) is a rare demyelinating disease that typically presents in immunodeficient patients. We report a case of a previously healthy 62-Year-Old woman who suffered from an unsteady gait, throbbing headaches, and progressive left-sided weakness and numbness. Stroke was initially suspected based on imaging and symptoms. A series of follow-up magnetic resonance images of the brain showed a right parietal lesion growing in size as the patient became unable to walk and experienced increasing lethargy and confusion. A biopsy of the lesion was positive for the John Cunningham virus (JCV). A diagnosis of PML was made and she was started on mefloquine. No improvement was seen on this treatment and her condition worsened. Although PML remains uncommon in immunocompetent individuals, it cannot be ruled out based on their immune status. Although the exact cause remains uncertain, underlying or transient states of immunosuppression may be responsible for reactivation of the JCV in these patients.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that typically occurs in immunosuppressed individuals. It is caused by reactivation of the John Cunningham virus (JCV) and infection of glial cells. It is often fatal, with a median life expectancy of less than six months following onset of symptoms [1]. Reports of PML afflicting immunocompetent patients are extremely rare but not unknown. We describe a patient with no previous medical issues and an intact immune system who presented with PML.

2. Case Presentation

A 62-year-old female with no past medical history presented to the emergency department after a one-month history of progressive left-sided numbness, weakness, and unsteady gait. She had also experienced multiple falls and bladder incontinence over the past two weeks. She complained of frequent throbbing headaches in the occipital area that were not relieved by analgesics. The patient denied fever, chills, confusion, visual changes, or seizures. She had not sought any medical attention prior to this point and was not on any medication. She was of Portuguese origin and was married with two adult children. She had previously worked as a salesperson. She had never smoked and had no history of illicit drug or alcohol use. She denied recent travel, sick contacts, or exposure to wildlife. Family history was unremarkable.

On examination, she was alert and oriented to person, time, and place. Some slight left-sided tongue deviation as well as decreased motor strength in the left upper and lower extremities was noted, including a mild drift of the left arm. Deep tendon reflexes were found to be normal. She had diminished light touch on the left side. Pupils were equal and reactive and extraocular movements were fully intact. Blood pressure was 145/75 mm Hg. Her lab work on admission was found to be normal, including a white blood cell count of 9000 cells/μL. Her electrocardiogram showed...
normal sinus rhythm. Computed tomography (CT) scan of
the head outlined an area of diminished attenuation in the
high right parietal lobe that was suspicious for edema. No
midline shift or mass lesions were noted.

Magnetic resonance imaging (MRI) was performed to
better characterize the CT findings (Figure 1). Multiple
abnormal areas were seen throughout the periventricular
and subcortical white matter of the bilateral cerebral hemispheres,
including the right parietal lobe region. No enhancement
was noted in these areas, making malignancy less likely. The
ventricles were normal in size and configuration. Carotid
Doppler ultrasounds did not show significant stenosis. A
transesophageal echocardiogram showed a normal ejection
fraction and no thrombi, with the presence of a patent
foramen ovale with a right-to-left shunt. The patient’s con-
dition did not show any improvement over the following
days and a follow-up brain MRI performed at this
time showed decreased perfusion of the right parietal area
in comparison to the contralateral side. Based on her CT
scan, MRI, echocardiogram, and neurological exam, acute on
superimposed chronic infarcts was suspected and the patient
was transferred to the inpatient rehabilitation unit ten days
following admission and placed on an antiplatelet agent.

During rehabilitation, her condition worsened. At day
15 of her hospitalization, she became unable to walk due
to worsening weakness of her left lower extremity and
experienced high fever. She also complained of occasional
vertigo. Her thinking became disorganized with diminished
attention. No rigidity, myoclonus, or cogwheeling was noted.
The patient’s leukocyte count was elevated to 18,900 cells/μL,
with 67% lymphocytes. Urine and blood cultures returned
negative. Anti-nuclear antibodies and rheumatoid factor
were negative. HIV status was negative on ELISA and poly-
merase chain reaction (PCR) testing. A CT of the abdomen
and chest revealed only mild hepatosplenomegaly. Follow-up
brain MRI showed a 0.5 centimeter increase in the diameter
of the right parietal lesion.

Due to lack of clear diagnosis, biopsy of the right
parietal lesion was performed, in addition to analysis of
the cerebrospinal fluid (CSF). This showed demyelinating
macrophages in addition to enlarged bizarre-shaped cells
with nuclear inclusions that stained positive for antibodies
against simian virus 40 (SV40). SV40 immunochemistry is
known to cross-react with the JCV [2]. A diagnosis of PML
was made based upon these findings. This was confirmed
by positive PCR and in situ hybridization results for JCV
from CSF samples were sent to the National Institute of
Health. She was started on a mefloquine trial, which had
previously shown some success in inhibiting JCV replication.
Unfortunately, she did not show any improvement while on
mefloquine and continued experiencing a decline in mental
function over the following four months. She ultimately
became comatose and died.

3. Discussion

It has been recognized that the JCV is highly prevalent in
the adult population, with 50–90% of healthy individuals
having been exposed to the virus [3]. Approximately 85% of
the population has antibodies to JCV. The virus’ purported
site of latency in the human body is currently under debate.
It is known that it not only establishes itself in the kidney
and bone marrow but also may be present in the brain
prior to reactivation [4]. Currently, about 75% of individuals
afflicted with PML have AIDS, 13% have hematological
malignancies, and 5% are organ transplant recipients [5].
Recently, PML has also been associated with the use of newer
immunomodulating medication such as natalizumab [6, 7],
rituximab [8], and efalizumab, representing 3% of cases [3].

Cases of PML in seemingly immunocompetent individu-
als are very uncommon. The exact cause of JCV reactivation
in patients who are not immunodeficient remains controver-
sial. A series of cases by Gheuens et al. showed that a certain
degree of mild immunosuppression was present in 38 cases
of individuals with PML who were HIV-negative and free of
malignancies. The associated conditions among this subset of
patients were variable and included hepatic cirrhosis, chronic
renal failure, dermatomyositis, pregnancy, and Alzheimer’s
disease, none of which were present in our patient [9]. In
addition, three patients were clinically suspected of having a
degenerative disease. A case report from Tan et al. described
a healthy patient with a CD4+ count of 1200 cells/μL who
was diagnosed with PML and recovered following a six-
month mefloquine treatment [10]. The role of mefloquine in
the patient’s recovery remains debatable as the clinical trial
was recently terminated after failing to show improvement in
subjects [10–12].

A case reported by Naess et al. was of a previously
healthy 35-year-old male with a CD4+ count of 994 cells/μL
who was diagnosed with PML by brain biopsy [13]. He
was treated with intravenous cidofovir and showed clinical
improvement as well as regression of white matter lesions on
MRI. Despite his treatment, it is suspected that his recovery
was spontaneous. Cidofovir, along with mefloquine, cytosine
arabinoside, and interferon alpha were not associated with

![Figure 1: Axial T2-FLAIR image shows increase in signal intensity in the subcortical white matter involving the U-fibers in the right parietal lobe.](image-url)
any survival benefits in patients with PML, despite some in vitro efficacy against JCV [3]. It appears that the body’s ability to mount a strong immune response to the JCV virus can result in disappearance of the disease [14]. This was shown in HIV-positive patients, where initiation of highly active antiretroviral therapy (HAART) was associated with the best prognosis [15].

It has been postulated that a transient dysfunction of the immune system caused by a subclinical viral infection may be responsible for reactivation of JCV within the setting of an immunocompetent individual [10]. However, there are no proven cases of this occurring and we do not have any reason to suspect this in our patient. Another possibility is idiopathic CD4+ lymphocytopenia, a rare condition that is defined as a documented CD4+ cell count of less than 300 cells/μL in HIV-negative patients. A recent review of the initial presentation of patients with idiopathic CD4+ lymphocytopenia by Zonios et al. described one case of PML among 39 individuals [16]. A T-cell subset count was not obtained in our particular case. However, complete lymphocyte counts were constantly found to be normal. Idiopathic CD4+ lymphocytopenia will usually present with absolute lymphocytopenia, making it an unlikely condition in our patient’s case.

The patient’s clinical course, radiographic findings, and histology were highly typical of PML, despite showing no signs of depressed immune function. The progression of the disease in this patient is unique, considering that previous immunocompetent cases with PML reportedly recovered following hospitalization. Although the effectiveness of pharmacological treatment has not been proven, it did not seem to alter the course of the disease in our patient. The cause of viral reactivation in her case remains unknown. The possibility of an undiagnosed degenerative disease cannot be excluded in her case although her younger age would make this less likely. PML may present in immunocompetent individuals although controversy remains as to whether a certain degree of immunosuppression, either transient or chronic, is required for this occurrence.

**Abbreviations**

PML: Progressive multifocal leukoencephalopathy  
JCV: John Cunningham virus  
CT: Computed tomography  
MRI: Magnetic resonance imaging  
HIV: Human immunodeficiency virus  
PCR: Polymerase chain reaction  
ELISA: Enzyme-linked immunosorbent assay  
SV40: Simian virus 40  
AIDS: Acquired immune deficiency syndrome  
HAART: Highly active antiretroviral therapy

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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