Lenalidomide-Associated Progressive Multifocal Leukoencephalopathy

Michael Ke Wang, MD1–3, Stefan D. Jevtic, MD1, Ryan Rebello, MD4, Adam S. Komorowski, MD3–5

1Department of Medicine, McMaster University, Hamilton, Canada; 2Population Health Research Institute McMaster, University, Hamilton, Canada; 3Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, Canada; 4Department of Diagnostic Imaging, McMaster University, Hamilton, Canada; 5Division of Medical Microbiology, Dept. of Pathology and Molecular Medicine, McMaster University

Corresponding Author: Michael Ke Wang: wangm7@mcmaster.ca

Submitted: 18 January 2023; Accepted: 5 May 2023; Published: 5 June 2023

DOI: https://doi.org/10.22374/cjgim.v18i2.687

Abstract
A man in his 80s with IgG kappa and free light chain multiple myeloma was admitted to hospital with several weeks’ history of falls and cognitive decline. Magnetic resonance imaging of the brain demonstrated bilateral lesions in the corona radiata, centrum semiovale, and corpus callosum. The suspicion for progressive multifocal leukoencephalopathy was raised due to his ongoing use of lenalidomide for multiple myeloma. A diagnostic lumbar puncture was performed, and polymerase chain reaction testing of his cerebral spinal fluid was positive for John Cunningham Virus. The patient was diagnosed with progressive multifocal leukoencephalopathy, and lenalidomide was stopped in consultation with his hematologist. The patient died three weeks after the diagnosis was established. Physicians should consider the diagnosis of progressive multifocal leukoencephalopathy in patients presenting with rapid cognitive decline and chronic use of immunosuppressive medications such as lenalidomide.

Résumé
Un octogénaire atteint d’un myélome multiple à chaînes légères libres et à IgG kappa est hospitalisé pour cause de chutes et d’un déclin cognitif observés depuis plusieurs semaines. Une IRM cérébrale révèle des lésions bilatérales dans la couronne rayonnante, le centre ovale de Vieussens et le corps calleux. On soupçonne la présence d’une leucoencéphalopathie multifocale progressive en raison de la prise continue de lénalidomide pour traiter le myélome multiple. Une ponction lombaire diagnostique est alors réalisée, et l’analyse par amplification en chaîne par polymérase (PCR) du liquide céphalorachidien révèle la présence du virus John Cunningham. Une leucoencéphalopathie multifocale progressive est donc diagnostiquée chez le patient, et la prise de lénalidomide est arrêtée en consultation avec son hématologue. Le patient est décédé trois semaines après l’établissement du diagnostic. Les médecins devraient envisager le diagnostic de leucoencéphalopathie multifocale progressive chez les patients présentant un déclin cognitif rapide et qui prennent des immunosuppresseurs, comme le lénalidomide, de façon chronique.

Keywords: progressive multifocal leukoencephalopathy; John Cunningham virus; multiple myeloma; lenalidomide
Case

A male patient in his 80s was admitted to the internal medicine ward with several weeks’ history of recurrent falls and progressive cognitive decline. He had been diagnosed with IgG kappa and free light chain multiple myeloma (MM) five years prior and was initially treated with 7 cycles of bortezomib, melphalan, and prednisone. He was subsequently transitioned to lenalidomide (10 mg orally daily) and dexamethasone (20 mg orally weekly) and had remained on this regimen with good response. His MM was in remission at the time of presentation. There was no previous history of any other immunocompromising conditions and no history of cognitive impairment. On collateral history, he was identified to have had multiple falls within the past month due to right leg weakness. His family had also noticed a rapid progression in word-finding difficulties, loss of interest, and forgetfulness. On examination, the patient was unable to follow commands. He demonstrated echolalia with perseveration and motor persistence. Additional neurologic findings included right-sided pronator drift, weakness in a pyramidal pattern, and severe ataxia. There were no other findings of weakness, altered sensation, or reflex abnormalities. Initial investigations did not reveal a clear etiology of his symptoms, and the patient’s symptoms continued to rapidly progress during his course of stay. Over the next two weeks, he was noted to have increased motor weakness, worsened mobility, and increased loss of interest and forgetfulness.

Laboratory investigations, including anti-nuclear antibody, human immunodeficiency virus (HIV) testing, and a paraneoplastic panel (i.e., Anti-Hu, Anti-Ri, and Anti-Yo) were negative. Computed tomography (CT) of the brain without contrast demonstrated no significant intracranial pathology. An MRI of the brain without contrast was performed, which identified low T1/high T2 lesions in the bilateral frontal-parietal lobes involving the centrum semiovale (Figure 1). Subsequently a magnetic resonance imaging (MRI) scan performed with gadolinium enhancement found additional lesions in the corona radiata, centrum semiovale, and corpus callosum. The lesions demonstrated T2 shine-through and did not enhance with gadolinium. The radiologist favored these imaging findings to represent changes related to chronic infarcts.

The radiologic diagnosis of multifocal chronic infarcts was felt to be inconsistent with the patient’s clinical presentation. The differential diagnosis included infectious encephalitis (i.e., tuberculosis, HIV, syphilis, cryptococcus, and John Cunningham Virus [JCV]), autoimmune encephalitis, and paraneoplastic encephalitis. In the literature, several immunosuppressing drugs had been previously associated with progressive multifocal leukoencephalopathy (PML), so this was considered the leading diagnosis. A diagnostic lumbar puncture was performed, and polymerase chain reaction (PCR) testing of the cerebral spinal fluid (CSF) was positive for JCV.

The inpatient neurology and infectious disease services were consulted, and the final diagnosis was determined to be PML secondary to lenalidomide use. Lenalidomide and dexamethasone were discontinued in consultation with his oncologist. Given the poor prognosis of PML, a decision was made with the patient’s family to focus on comfort measures. Plasmapheresis and other drug therapies were not considered as part of his disease management due to his goals of care. The patient was discharged home with palliative care services. The patient’s cognition rapidly deteriorated, and he passed away three weeks later.

Discussion

PML is an often-fatal demyelinating infection of the central nervous system caused by the reactivation of JCV. JCV is ubiquitous in the general population and is thought to spread via oral/respiratory transmission. Observational data suggest that 60 to 80% of individuals will have serologic evidence of infection by the age of 60. While initial infection with JCV is typically asymptomatic, life-threatening neurological complications can later ensue in immunocompromised patients, particularly when viral reactivation occurs or when a chronically detectable viral load is present. Approximately 15 to 30% of JCV reactivations leading to PML are reported in patients with HIV, with other notable associations including hematologic malignancies (e.g., chronic lymphocytic leukemia), transplant recipients, autoimmune diseases, and those receiving novel biologic therapies.

Classic PML manifests as subacute neurologic changes, including progressive mental status deterioration, motor deficits (including paresis), and ataxia. However, patients may present with a variety of manifestations, including aphasia and seizures, due to the diffuse pattern of viral reactivation. In our case, the patient initially presented with nonspecific symptoms of cognitive decline and was first diagnosed with delirium. However, uncertainty arose from accumulating evidence discordant with our provisional diagnosis, ultimately leading to the pursuit of alternate etiologies.

MRI may reveal multifocal, asymmetric, non-enhancing lesions throughout the brain, with lesions classically being
Lenalidomide-associated PML

have now suggested an association between PML and lenalidomide use. This is believed to be secondary to the chronic state of immunosuppression induced by lenalidomide, as opposed to being caused by MM itself. In our case report, the M-protein (paraprotein) level was found to be stable before hospital admission, implying minimal MM activity at the time PML was diagnosed. We conducted a review of the literature and identified a total of seven cases (including our own) of PML associated with lenalidomide use in multiple myeloma (Table 1).

Of these patients, five died within four months of their diagnosis.

The cornerstone of therapy is to reverse the state of immunosuppression. This is usually achieved by initiating anti-retroviral therapy in HIV patients and by discontinuing immunosuppressive medications where applicable. In patients with organ or bone marrow transplantation, case reports suggest a net favorable outcome in mortality with medication discontinuation, despite the increased risk of rejection. An informed discussion with patients and family members is crucial in these situations. We discontinued

![Figure 1. Axial fluid-attenuation inversion recovery (FLAIR) (A) and diffusion-weighted imaging (DWI) (B) from magnetic resonance imaging of the brain. The axial FLAIR image demonstrates confluent high signal intensity within the affected areas. The DWI and corresponding Apparent Diffusion Coefficient (ADC) map demonstrate asymmetric high signal intensity within the deep frontal white matter on the DWI image without corresponding reduction in ADC value. No central or peripheral enhancement is present around the white matter abnormality on the post-gadolinium axial T1-weighted image (not shown).]
Table 1. Summary of Case Reports Describing Multiple Myeloma Patients with Progressive Multifocal Leukoencephalopathy in Association with Lenalidomide Use

<table>
<thead>
<tr>
<th>Study</th>
<th>Case Presentation</th>
<th>Maintenance Therapy</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2019</td>
<td>60F diagnosed with MM 4 years prior, presenting with left-sided dyspraxia, expressive dysphasia, incontinence</td>
<td>Lenalidomide and dexamethasone for the past 47 months</td>
<td>Immunosuppression ceased. Oral mirtazapine 15 mg daily</td>
<td>Death 4 months after diagnosis</td>
</tr>
<tr>
<td>Brigo 2017</td>
<td>60M diagnosed with MM 3 years prior, presenting with progressive altered mental status left-sided hemiparesis</td>
<td>Lenalidomide 5 mg daily for the past 9 months</td>
<td>Immunosuppression ceased</td>
<td>Death 2 months after diagnosis due to pneumonia/sepsis</td>
</tr>
<tr>
<td>Knight 2020</td>
<td>59M diagnosed with MM 14 years prior, presenting with 3 weeks of memory impairment, aphasia, behavioral changes</td>
<td>Lenalidomide for the past 2 years</td>
<td>Immunosuppression ceased Palliative measures</td>
<td>Death 2 weeks after admission</td>
</tr>
<tr>
<td>Nishimura 2020</td>
<td>71M diagnosed with MM 5 years prior, presenting with progressive visual disturbance, abnormal behavior, cognitive impairment</td>
<td>Lenalidomide 25 mg daily and low-dose dexamethasone for the past 2 years</td>
<td>Immunosuppression ceased Oral melfloquine</td>
<td>Alive 1 year after diagnosis Able to independently walk and eat, but no improvement in cognition</td>
</tr>
<tr>
<td>Ruiz-Heredia 2019</td>
<td>73F diagnosed with MM 20 months prior, presenting with left-sided hemiparesis progressing to hemiplegia</td>
<td>Lenalidomide with low-dose dexamethasone following induction phase</td>
<td>Not described</td>
<td>Rapid decline in level of consciousness followed by death</td>
</tr>
<tr>
<td>Usui 2020</td>
<td>73M diagnosed with MM 3 years prior, presenting with left-sided hemiparesis, facial palsy, spatial neglect, and dysarthria</td>
<td>Lenalidomide 25 mg daily, dexamethasone, and elotuzumab</td>
<td>Immunosuppression ceased Oral melfloquine 27.5 mg weekly Mirtazapine 15 mg daily</td>
<td>Gradual neurologic recovery with no evidence of progression on MRI and CSF at 6 months</td>
</tr>
<tr>
<td>Wang 2023</td>
<td>80M diagnosed with MM 5 years prior, presenting with cognitive decline, right-sided hemiparesis, and echolalia</td>
<td>Lenalidomide (10 mg daily) and dexamethasone (20 mg weekly) for past 5 years</td>
<td>Immunosuppression ceased Palliative measures</td>
<td>Death 3 weeks after diagnosis</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid; MM: multiple myeloma; MRI: magnetic resonance imaging.

lenalidomide and dexamethasone therapy after discussions with the patient’s oncologist and family.

Specific conditions may benefit from additional management strategies. For example, in patients with natalizumab-associated PML, plasmapheresis can be used to hasten clearance of the drug. However, a recent literature review of 219 cases failed to demonstrate any clinical benefit of plasmapheresis. In cases of PML-IRIS, glucocorticoids have been used when there is a significant neurologic deterioration or mass effect, though its efficacy remains unproven. Small clinical trials have failed to demonstrate any benefit with using melfloquine, cytarabine, or cidofovir. While some case reports have described success with treating PML with mirtazapine, no high-quality data supports its efficacy. Ultimately, there is limited evidence that any of these therapeutic strategies improve patient outcomes.

The prognosis varies considerably based on the underlying etiology of disease and whether the underlying immunosuppressive state is reversible. Patients with natalizumab-associated PML have the highest survival rate (>80% at one year), followed by HIV-associated PML treated with anti-retroviral therapy (>50% at one year). PML associated with hematologic malignancies have the poorest prognosis, with an estimated median survival of three months. Those treated with hematopoietic stem cell transplant tend to survive longer when compared to chemotherapy or immunotherapy-treated patients (median survival 8 versus 2 months).
Conclusion

PML is a severe viral reactivation syndrome often associated with immunosuppressive conditions or medications. PML is rarely associated with lenalidomide use in patients with MM and carries a poor prognosis in this setting. PML should be considered in immunosuppressed patients presenting with rapidly progressive dementia and an abnormal brain MRI. The diagnosis of PML ultimately requires confirmation of JCV in a CSF or tissue sample, and management of the disease should primarily focus on reversing the underlying state of immunosuppression.

Conflicts of Interest

We declare no conflicts of interest.

Sources of Funding

We declare no sources of funding for this study. Dr. Wang is supported by the PSI Foundation – Research Trainee Award.

Informed Consent

Written informed consent was obtained from the patient’s next of kin to publish this case report.

Ethics Approval

None required for a case report.

Contributions

All authors contributed to draft, reviewed and edited the manuscript, and approved the final version.

References