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Case report

# Pembrolizumab for the treatment of Progressive Multifocal Leukoencephalopathy (PML) in a patient with AIDS: A case report and literature review

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is an opportunistic central nervous system (CNS) infection caused by the reactivation of John Cunningham polyomavirus (JCV) from suppression of the host immune system due to conditions such as human immunodeficiency virus causing acquired immunodeficiency syndrome (HIV/AIDS), hematological malignancies, multiple sclerosis, and use of immunosuppressant medications. Pembrolizumab is an immune checkpoint inhibitor targeting programmed cell death protein-1 (PD-1) receptors on lymphocytes. In recent years its use is expanding to treat several malignancies and it is a drug of interest for the treatment of PML. In this case report, we present a case of an HIV/AIDS patient who was given a trial of pembrolizumab for treatment of PML. We also provide a literature review of the reported cases of use of this medication in other immunocompromised states.

## Introduction

Pembrolizumab is an immune checkpoint inhibitor with expanding indications for the treatment of tumors expressing PD-L1 or PD-L2, which are ligands for the programmed cell death 1 (PD-1) receptor on activated T cells. The binding of PD-L1 or PD-L2 to PD-1 leads to the inhibition of the cytotoxic T cell response. It is hypothesized that in PML patients, an immune checkpoint protein, PD-1 expression is increased in CSF CD4 + and CD8 + lymphocytes. Therefore, the use of pembrolizumab, a PD-1 inhibitor is an area of interest and this medication has been used with variable outcomes in cases of PML.

## Case

A 64-year-old Caucasian male with a past medical history of non-small cell lung cancer (NSCLC) (status post radiation therapy 5 years prior), chronic obstructive pulmonary disease, pulmonary embolism on rivaroxaban presented to the emergency department with worsening bilateral visual loss in the left field of vision for 4 weeks. On prior outpatient evaluation, there was initial concern for glaucoma but later there was suspicion of a central nervous system pathology prompting his arrival to the emergency department for further evaluation. He reported unintentional 30-pound weight loss over 2 months along with a progressive decline in short-term memory. He also reported recent falls due to subjective lower extremity weakness. He denied numbness, tingling, difficulty swallowing, slurred speech, difficulty finding words, headache, sleep disturbances, dizziness, nausea, vomiting, and bowel or bladder dysfunction. Vital signs were within the normal range. Physical examination was pertinent for left homonymous hemianopsia.

Initial laboratory workup including total blood count, electrolytes, lipid panel, TSH, HbA1C, ESR, vitamin B12, and folic acid was within normal range. C-reactive protein was mildly elevated 1.45 m/dl. MRI brain showed extensive, multifocal white matter signal abnormalities with subcortical U-Fiber involvement and sparing of adjacent gray matter with white matter lesions in the right hemisphere that were T2 hyperintense, T1 hypointense which did not enhance with gadolinium administration (Fig. 1). The imaging findings were strongly suggestive of PML, but differential diagnosis included viral encephalitis and acute

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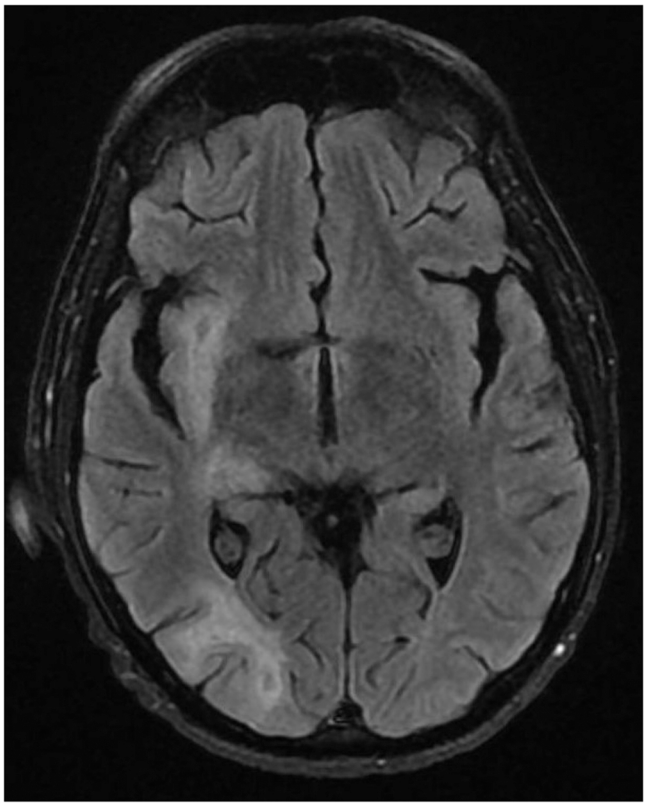

**Fig. 1. Legend:** Magnetic resonance image of brain showing confluent increased FLAIR signal intensity involving the subcortical and periventricular white matter and sparing of gray matter of the right parietal-occipital lobes and right temporal lobe.

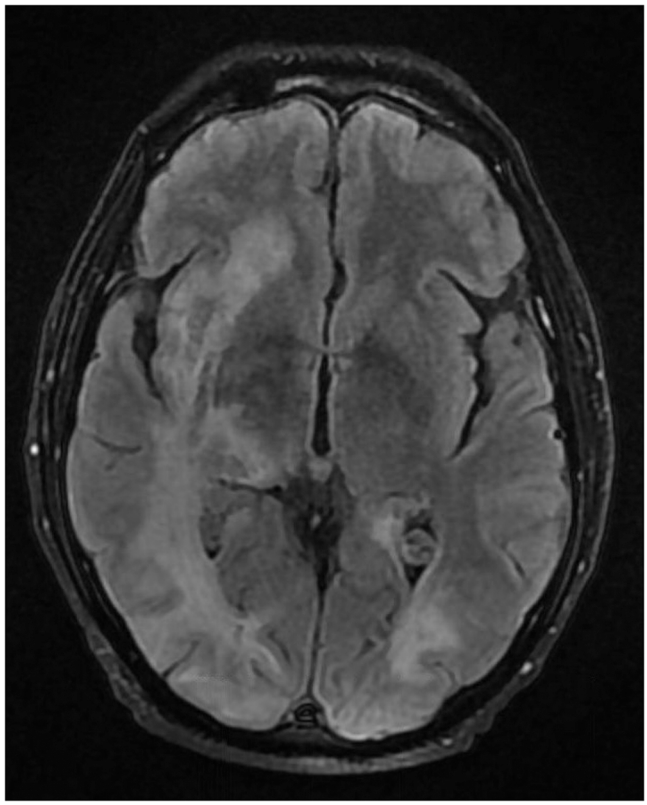

**Fig. 2. Legend**: Follow-up magnetic resonance imaging showing interval progression of foci primarily white matter signal abnormality, involving the right greater than left hemisphere, with involvement of the splenium of the corpus callosum, extension to the parietal occipital white matter.

disseminated encephalomyelitis.

The patient tested positive for Human Immunodeficiency Virus (HIV) using the 4th generation screening assay. HIV-1 viral load was 267,501 copies/ml, absolute cluster of differentiation 4 (CD4) cell count was 58/ $mm^3$ with CD4% 4%. Serology was positive with plasma JCV PCR showing $<$ 500 copies/ ml. The autoimmune encephalitis panel was negative. Other infectious workups for syphilis, tuberculosis, gonorrhea, chlamydia, toxoplasmosis, cytomegalovirus and hepatitis were negative. Further inquiry revealed that the patient had a needle stick injury during his work in a laboratory many years ago. Antiretroviral therapy with once-daily fixed-dose Abacavir-Dolutegravir-Lamivudine was initiated along with trimethoprim-sulfamethoxazole regimen for Pneumocystis jerovecii prophylaxis. He was discharged home and lumbar puncture was performed as an outpatient. CSF analysis was positive for JCV on qualitative PCR. A definite diagnosis of PML was made at this time based on the overall clinical picture.

Two months after initial admission, the patient was re-admitted for left-sided weakness, declining functional status, repeated falls, and worsening vision loss. The patient's presentation was consistent with the progression of PML supported by the progression of white matter lesions on repeat brain MRI [Fig. 2]. There was no contrast enhancement thus immune reconstitution inflammatory syndrome (IRIS) was considered less likely. Repeat Lumbar puncture showed CSF normal protein and glucose levels, 5 nucleated WBC, 119 RBCs. CSF VDRL, HSV − 1 and − 2 PCR, cryptococcus antigen testing were negative. Serum fungal antibodies for Histoplasma, Blastomyces, Aspergillus, and Toxoplasmosis were negative. CD4 cell count had improved from the prior 58–144/ mm3 from the time of HIV diagnosis. Intravenous (IV) Pembrolizumab 2 g/kg was started for compassionate use with plans to repeat every 4 weeks. Even after a week, there was no improvement in left hemiparesis and patient developed left hemineglect. He also developed hospital acquired pneumonia for which was treated with piperacillin-tazobactam. Due to deteriorating neurological status, a repeated brain MRI was performed which showed further progression of PML (Fig. 3). There was now localized mass effect and edema which were concerning for PML-IRIS. Dexamethasone 8 mg every 6 h was started with only a slight improvement in left-sided strength. The patient developed Clostridioides difficile colitis and oral vancomycin was initiated. Eventually, the patient was transitioned to hospice care and passed away.

## Discussion

Progressive multifocal leukoencephalopathy (PML) is an opportunistic central nervous system (CNS) caused by the JCV in immunocompromised patients. JCV is ubiquitous in human beings with antibodies found in up to 70% of healthy individuals. The virus is known to be latent in kidney tissues in healthy subjects but it undergoes reactivation with genetic rearrangement on development of immunocompromised state which makes the virus neurotropic [1]. The virus causes demyelinating lesions in the central nervous system. Helper T cells have a major role in inhibiting the reactivation of JCV, thus depletion of T cells is a harbinger of JCV reactivation [1,2]. PML is classically associated with HIV but is also seen in Multiple sclerosis (MS), hematological malignancies, organ transplant, and autoimmune deficiency states. In recent years immunomodulatory drugs like natalizumab, obinutuzumab, and rituximab have been associated with PML [3]. There is an increasing number of PML cases being reported in lymphoproliferative disorder patients treated with monoclonal antibodies causing depletion of the B cell population [2].

PML manifests as various neurological deficits and is a progressive condition unless immune reconstitution is achieved [4]. Initiation of antiretroviral therapy in HIV patients and withdrawal of

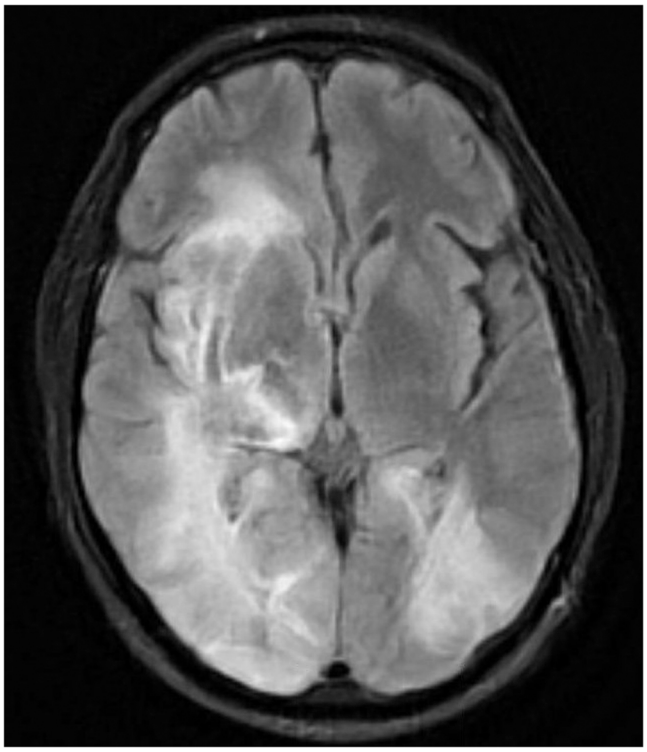

**Fig. 3. Legend**: Follow up magnetic resonance imaging of the brain showing extension of FLAIR signal to the right frontal lobe, temporal lobe, and parietal occipital lobes. Progression of confluence across the midline via the splenium of the corpus callosum with involvement of the left posterior temporal-parietal occipital noted.

immunosuppressive medications in MS patients can help achieve immune reconstitution but in patients with hematological malignancy and primary immunodeficiency, it is difficult to achieve immune reconstitution [5]. With the increasing use of the monoclonal antibody in lymphoproliferative disorder and autoimmune disorders, the incidence of PML seems to have risen in this population. [6].

Currently, there are no known effective therapeutic drugs available for PML. Recently, the anti-PD-1 immune checkpoint inhibitor, pembrolizumab has been the drug of interest for the treatment of PML [4]. It is seen that in PML patients, an immune checkpoint protein called programmed cell death protein 1 (PD-1) expression is increased in CSF CD4 + and CD8 + lymphocytes and on macrophages of PML lesions [1, 7]. PD-1 protein interacts with its ligands on antigen-presenting cells leading to negative regulation of T cell activation [5]. Pembrolizumab is an immune checkpoint inhibitor, targeting PD-1 proteins [3,8]. By blocking the PD-1 ligand interaction, pembrolizumab leads to increased activation of T cells [5]. It has been established that in HIV patients there is high PD-1 expression on T cells leading to reduced activation of the T cells [9]. PD-1 expression is also found to be enhanced in CD4 + and CD8 + T lymphocytes in CSF in PML patients [10], thus there is the inability to clear the JC virus. Pembrolizumab can also increase levels of JCV-specific CD8 + cytotoxic T lymphocytes [11]. Based on this pathophysiology of the disease, PD-1 inhibitors have been tried to treat PML.

According to our literature review, there are 28 reported cases (excluding our case) where pembrolizumab therapy has been attempted to treat PML The underlying etiology of immune system compromise in these patients is varied including HIV, genetic immune deficiency syndromes, lymphoproliferative malignancy, chemotherapy especially CD 20 inhibitors. There are only 3 reported cases of pembrolizumab used in PML patients with HIV [Table 1] [1,12]. All other PML cases with causes of immune compromise other than HIV, treated with pembrolizumab are listed in Table 2 [1,3–5,7,10,11,13–17]. Overall, 17 out of 28 cases had reported improvement or stabilization of neurological symptoms.

Muzo et all reported successful treatment of PML in an HIV patient with 3 doses of pembrolizumab, each 4 weeks apart with improvement in neurological symptoms of dysarthria and ataxia and JCV clearance from CSF after the first dose. At the time of diagnosis, this patient had HIV RNA $<$ 20 copies/ml, 120 $CD4^+/mm^3$, $CD4^+$ 10%, $CD4^+/CD8^+$ ratio 0.20 [12].

Cortese et al. in their cohort of 8 patients with PML reported successful treatment of PML in 2 HIV patients. A 48 yr old female with a diagnosis of HIV, 20 years prior to PML diagnosis. She was initially on antiretroviral therapy, which she discontinued and was started again 4 years prior to PML presentation. Her absolute CD4 count was 156, and CSF JCV viral load was 63 copies/ml at the time of presentation. Symptoms of cortical motor aphasia and left arm weakness improved substantially with 2 doses of pembrolizumab with clearance of JCV from CSF [1]. The other case was of a 58 yr old male diagnosed with HIV, 21 years ago while on antiretroviral therapy. He had an undetectable HIV viral load, with an absolute CD4 count of 580, and CSF JCV viral load of 286 copies/ml and presented with truncal and appendicular ataxia with associated dysarthria. With 2 doses of pembrolizumab, there was a stabilization of symptoms but after the 3rd dose there was a clinical improvement and the JCV load decreased to 96 copies/ml. To the best of our knowledge, our case is the 4th reported case of pembrolizumab use for PML in HIV patients. Unfortunately, our patient did not respond to pembrolizumab and there was progressive neurological decline and he eventually died. With the paucity of data, it is not clear what factors lead to the improvement of PML in the previously reported three HIV patients. As compared to previous cases, our patient was older and had an advanced stage of HIV/AIDS at the time of presentation with high HIV viral load which likely led to the poor outcome. We were unable to obtain quantitative JCV viral load in the CSF of our patient from our reference lab (Mayo Clinic Laboratories, Rochester, MN, USA). In the last MRI brain of our patient prior to his death, there was some evidence of edema and mass effect concerning for the development of IRIS. None of the patients in the 8-patient series reported by Cortese et al. had IRIS and the authors attributed it to persistent lymphopenia in their patient cohort [1] which was not the case in our patient.

High viral loads of JCV are associated with negative outcomes of PML independent of pembrolizumab treatment and hence an early introduction of the drug may have beneficial effects [13]. Cortese reported that decreased expression of PD-1 was an indicator of successful treatment as 5 of the 8 patients who improved also had a decline in JCV viral load [1]. Pawlitzki et al. reported against as their patient had decreased PD-1 expression, but still had an unfavorable outcome. [13].

**Table 1**
Summary of reported cases of HIV/AIDS treated with pembrolizumab.

| Serial number | Author | h/o HIV / AIDS | JCV viral load on presentation copies/ml | Age/ Sex | Doses of pembrolizumab received | Previous immunosuppressants used | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Cortese 2019[1] | HIV | 286 | 58/M | 3 | Efavirenz, emtricitabine, tenofovir | Clinical improvement after 3rd dose |
| 2 | Cortese 2019[1] | HIV | 63 | 48/F | 2 | HAART | Improved |
| 3 | Mozo 2019 [12] | HIV | Not available | 44/F | 3 doses 4 weeks apart | | Improved JCV cleared from CSF |

**Table 2**
Summary of reported cases of PML in immunocompromised host due to etiology other than HIV/AIDS where pembrolizumab was used.

| Serial number | Author | h/o HIV / AIDS | JCV viral load on presentation copies/ml | Age/ Sex | Doses of pembrolizumab received | Previous immunosuppressants used | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Cortese 2019[1] | CLL | 232 copies/ml | 67/ M | 3 | Fludarabine Cyclophosphamide rituximab | No improvement |
| 2 | Cortese 2019[1] | CLL | 6044 copies/ml | 78/ M | 2 | Fludarabine Cyclophosphamide Rituximab Ibrutinib Mycophenolate | Stabilization of symptoms and then improvement |
| 3 | Cortese 2019[1] | Non-Hodgkin's lymphoma | 26494 | 69/F | 1 | Chemotherapy, Rituximab | Neurological decline |
| 4 | Cortese 2019[1] | Idiopathic lymphopenia | 5248 | 31/ M | 3 | None | Improvement |
| 5 | Cortese 2019[1] | Common variable immunodeficiency | 28350 | 62/F | 2 | Prednisone, Methotrexate, TNF inhibitor | Neurological decline |
| 6 | Cortese 2019[1] | Hodgkin's lymphoma | 261 | 70/ M | 1 | Chemotherapy, radiation | Improvement |
| 7 | Darcy 2020 [3] | Rheumatoid arthritis | log 3.11 copies/ ml. | 60/ M | 2, 3 weeks apart | Rituximab mefoquine cytarabine | Neurological decline |
| 8 | Darcy 2020 [3] | CLL | Brain biopsy showed JCV | 78/ M | 2 | chlorambucil Obinutuzumab | Died |
| 9 | Möhn 2021 [4] | Mantle cell lymphoma | CSF negative, brain biopsy positive | 78/ M | 3 | rituximab/bendamustine | Neurological decline |
| 10 | Möhn 2021 [4] | Immunocytoma | CSF negative, brain biopsy positive | 73/ M | 3 | Mefloquine, immunoglobulin | Improved |
| 11 | Möhn 2021 [4] | B cell NHL | 500 copies/ml | 70/F | 2 | rituximab/bendamustine | Died |
| 12 | VolK 2021 [5] | CD-40 ligand deficiency | 471 | 21/ M | 3 | – | Stabilization |
| 13 | Volk 2021 [5] | Common variable immunodeficiency | Negative in CSF, positive in brain biopsy | 45/F | 4 | Immunoglobulin Budesonide Rituximab | Stabilization of PML symptoms, death due to autoimmune complications) |
| 14 | Volk 2021 [5] | Diffuse large B cell lymphoma | < 500 | 78/ M | 1 | Rituximmab | Stable regarding PML (Death due to an unrelated cause- lymphoma) |
| 15 | Volk 2021 [5] | Combined immunodeficiency | 500 | 45/ M | 3 | – | Died |
| 16 | Volk 2021 [5] | Common variable immunodeficiency, Diffuse large B cell lymphoma | 1150 | 49/ M | | | stabilization |
| 17 | Holmes 2020[7] | Diffuse large B cell lymphoma | CSF detection, viral load not available | 68/F | 3 | Rituximab, Immunoglobulin Mefloquine | Stabilization |
| 18 | Küpper 2019[10] | Primary immundeficiency | 38 | 43/ M | 5 | | Died |
| 19 | Rauer 2019 [11] | Variable immunodeficiency Large B cell lymphoma | 119,000 | 49/ M | 5 (every other week) | Chemotherapy, rituximab | Stabilization |
| 20 | Pawlitzki 2019[13] | Combined immunoglobulin deficiency Bechet's disease | Not available | 38/ M | 2 | immunoglobulin | Died |
| 21 | Kapadia 2020[14] | Diffuse large B cell lymphoma | Not available | 69/F | 4 | | Improved |
| 22 | Mahler 2020[15] | DLBCL | 449 | 33/F | 1 | Received IL-2 prior to pembrolizumab | Stabilized |
| 23 | Mahler 2020[15] | DLBCL | 309 | 60/ M | 2 | RCHOP Received IL-2 prior to pembrolizumab | Improved |
| 24 | Goercin 2020[16] | No underlying immunodeficiency state | Not available | 71/ M | 5 | Received IL-2 prior to pembrolizumab | Improved PML symptoms but died of respiratory conditions |
| 25 | Stogbauer 2021[17] | Diffuse largeB cell lymphoma | 3500,000 copies/ ml | 54/F | 3 | R-CHOP | Died |

Data on pembrolizumab use in PML is very limited currently. In theory, there are a number of factors that can affect patient outcome including characteristics of age, gender, co-morbidities, etiology of immune suppression, and JCV viral load at the time of PML diagnosis. Further large scale studies are thus needed to determine the effectiveness of pembrolizumab in PML.

## Author contribution

Tulika Chatterjee: Literature search, Manuscript writing. Moni Roy: Manuscript writing. Rone-Chun Lin: Patient care, Manuscript writing. Sharjeel Ahmad: Patient care, Manuscript writing

## Ethical approval

This is not aresearch paper, ethical approval not applicaple

## Consent

Patient was deceased before we started writing the paper. We have

made sure that there are no identifier in any part of our manuscript

## Conflict of interest

None.

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