

**Bridging the Gap: Immunotherapy in Progressive Multifocal Leukoencephalopathy**

**A New Hope?**

Tristan Born, BM, Paola Vassallo, MD, Dela Golshayan, MD, PhD, Giovanni Di Liberto, MD, PhD, Jean-Philippe Brouland, MD, Kristof Egervari, MD, PhD, Doron Merkler, MD, Renaud A. Du Pasquier, MD, and Raphael Bernard-Valnet, MD, PhD

*Neurology*® 2023;101:e1382-e1386. doi:10.1212/WNL.0000000000207533

**Abstract**

Progressive multifocal leukoencephalopathy (PML) is a severe infection of the CNS occurring in immunocompromised individuals in which large demyelinating lesions are induced by...

From the Neurology Service (T.B., P.V., G.D.L., R.A.D.P., R.B.-V.), Department of Clinical Neurosciences, Transplantation Center (D.G.), Department of Medicine, and Pathology Department (J.-P.B.), Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and the University of Lausanne; and Service of Clinical Pathology (K.E., D.M.), Department of Pathology and Immunology and Diagnostic Department, University Hospitals of Geneva, Switzerland.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
polyomavirus JC (JCV). In the absence of effective antiviral treatment, control of the infection relies on restoring anti-JCV immunity. Thus, particularly in long-standing immunocompromising conditions such as organ transplantation, lymphoproliferative disorders, or idiopathic lymphopenia, new strategies to boost anti-JCV immune responses are needed. Here, we report the case of a patient developing PML in the context of kidney transplantation who received recombinant human interleukin 7 to foster immune responses against JCV. We give an overview of the immunologic mechanisms underlying the development of PML and immune restoration within the CNS after JCV infection. Immunotherapeutic strategies developed based on current understanding of the disease hold promise in managing patients with PML.

**Case Report**

A 78-year-old man with end-stage renal failure underwent renal transplantation in July 2021. His immunosuppressive regimen included tacrolimus, mycophenolate mofetil, and prednisone. Six months after transplantation, the patient developed subtle production aphasia. Brain MRI demonstrated multifocal frontal subcortical T2 hyperintense/T1 hypo-intense lesions without contrast enhancement (Figure, A–C) that were initially mistaken as an ischemic stroke. After 5 days, symptoms worsened and progressive multifocal leukoencephalopathy (PML) was confirmed by detecting JC virus (JCV) in the CSF (200 copies/mL). Consequently, maintenance immunosuppression was minimized, and a total of 2 g/kg IV immunoglobulins were given to prevent transplant rejection. Twelve days after the first MRI, the patient exhibited significant psychomotor slowing, mild aphasia, and proportional rightsided hemiparesis prompting a second MRI which showed enlargement of PML lesions without contrast enhancement. Given severe lymphopenia (0.27 g/L) and the absence of signs of immune reconstitution, a recombinant human interleukin 7 (rh-IL-7, CYT107, RevImmune) to foster anti-JCV immune response was started 25 days after disease onset. This treatment allowed a rapid restoration of lymphocyte count (1.75 g/L) within 10 days from treatment initiation. In parallel, the transplanted kidney was removed to avoid acute rejection. The patient subsequently developed a febrile condition with caecal ischaemia and agranulocytosis of unknown origin, treated empirically with piperacillin/tazobactam. A few days later, he developed severe anemia and abdominal CT scan showed hemorrhagic effusion in the nephrectomy lodge. Given predicted long-term neurologic sequelae and overall abdominal evolution, the family and medical team decided to transition to palliative care. The patient died 7 weeks after PML onset.

**Discussion**

This case highlights challenges in treating PML, especially in patients with sustained immunosuppression. PML is a rare opportunistic infection occurring in immunocompromised individuals including those with HIV, idiopathic CD4+ lymphopenia, hematological malignancies, or receiving treatment with immunosuppressive/immunomodulatory agents. The clinical presentation of PML, as described in this case, is usually sub-acute and may encompass cognitive or speech impairment, motor or sensory dysfunction, or ataxia. The classical radiologic and pathologic presentation for PML is shown in Figure. PML results from reactivation of JCV. The nonpathogenic form (archetype JCV) of the virus is transmitted from person to person and infects the oropharynx before spreading hematogenously to distant organs such as kidneys, bone marrow, or brain where it establishes latency/nonpathogenic persistent infection. In the context of immune suppression, the virus proliferates and accumulates sequence variations, leading to the creation of neurotropic rearranged (prototype) JCV. Then, after a second hematogenous spread or direct reactivation within the brain, this rearranged JCV can cause a lytic infection of brain cells. Oligodendrocytes, notably implicated in the generation and the maintenance of CNS myelin sheath, are particularly vulnerable, leading to extensive white matter involvement seen both on MRI and in postmortem pathology (Figure).

**Immunologic Mechanisms of Infection Control and Reactivation**

Virus control relies primarily on cellular immunity as demonstrated in this case by the CD3+ T-cell infiltration (encompassing both CD4+ and CD8+ T cell subsets) seen at the edge of the lesion (Figure, J). Infiltration is dominated by CD8+ T cells, with cytototoxic granules (granzyme B) polarized toward JCV-infected CNS cells. CD8+ T cells’ transmigration to the CNS seems to occur because of the CCR5 tissue-homing cue. CD8+ cytotoxic T lymphocytes are instrumental in JCV control because they are found in the vast majority of PML survivors. On the other hand, CD4+ T helper (Th) cells likely also play an important role as reactivation occurs mainly in patients with CD4 T-cell deficiencies. Th1, and to a lesser extent bifunctional Th1-Th2 cells, produce interferon-γ (IFN-γ) and IL-4 within the infected brain and promote viral clearance. Indeed, IFN-γ is a key regulator of the phagocytic activity of microglia and induces the
expression of MHC class II and costimulatory molecules which allow them to function as antigen-presenting cells for infiltrating T cells. Furthermore, IFN-γ stimulates expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and chemokines such as CCL2, CXCL9, and CXCL10 by astrocytes, which may facilitate T cells recruitment to the brain. This instrumental pathway could be affected in some patients with PML who display abnormal CD4+ T-cell responses against JCV with a lack of IFN-γ production. The production of IL-4 is more unexpected and could participate in viral clearance by stimulating both humoral immunity and CD8+ T cells. IL-4 may also have a neuroprotective role by enhancing neuronal survival and recovery.

Furthermore, as in other infectious diseases, T cells in PML may exhibit an exhausted phenotype. Exhaustion is a state of immune dysfunction characterized by the expression of inhibitory receptors such as the programmed cell death protein (PD)-1 leading to reduced cytokines production and cytotoxicity.

The role of B cells in anti-JCV responses has been detailed elsewhere and will not be covered here.

**Immune Reconstitution Inflammatory Syndrome**

To date, the best therapeutic option for PML relies on rapid restoration of immunity. Yet, immune response recovery is a double-edged sword because it may cause immune reconstitution inflammatory syndrome (IRIS) in a substantial proportion of patients. IRIS consists of a dysregulated anti-JCV immune response within the CNS, notably mediated by the cytotoxic activity of CD8+ T cells toward infected cells. It involves nonspecific tissue destruction induced by blood-brain barrier dysfunction, edema, and activation of macrophages and microglia. Clinically, IRIS is defined as a paradoxical deterioration in clinical status with specific MRI features not seen in PML (contrast enhancement, edema, mass effect). Management of PML-IRIS relies on corticosteroids. Targeted strategies to block the migration of CCR5+ CD8+ T cells have failed to demonstrate a beneficial effect. In transplant recipients, it is unclear whether rapid immune reconstitution could induce graft rejection. To prevent such acute rejection, we decided, in this case, to prophylactically explant the grafted kidney.

**Immunotherapies in PML**

Although restoration of anti-JCV immune responses is crucial for PML treatment, it remains challenging in patients with long-standing immunosuppression such as organ transplant recipients leading to a direct impact on prognosis. Understanding the immunologic mechanisms underlying PML opened a new era. Indeed, immunologic treatments/strategies have been repurposed to reinvigorate anti-JCV immune responses. In this case, we concomitantly withdrew immunosuppressing drugs and initiated rh-IL-7 hoping to allow immune reconstitution in the periphery and the CNS (Graphical Abstract). Rh-IL-7, previously developed for sepsis, is a crucial cytokine for T-cell...
maturation that stimulates the proliferation of naive and memory T cells including JCV-specific ones. Rh-IL-7 might then improve survival and prognosis in PML. We favored IL-7 based on its safety, the main adverse effect being injection site reactions and transient flu-like symptoms, and a lower rate of IRIS (5.8%).13 Given the immune reconstitution observed in this case (both in the periphery and on CNS pathology), we could suggest that rh-IL-7 was sufficient to reinvigorate anti-JCV responses. However, our patient’s poor outcome illustrates that time to introduce treatment is likely key to prevent severe neurologic damage.

Two other immune strategies have been recently proposed. First immune checkpoint inhibitors (ICIs), which have expanding indications in cancer, may improve PML outcomes. The rationale relies on blocking PD-1 on JCV-specific T cells, thus stimulating their proliferation and clearance of the virus. A very low number of T cells at baseline and the phenotype of terminal exhaustion have been associated with treatment failure.12 Yet, ICIs were associated with frequent (30%) immune-related adverse events (i.e., colitis, pneumonitis) and IRIS (19%).14

Second, JCV-specific T-cell transfer has been the most promising strategy so far, but its availability remains limited to a few expert centers.12,15 In this treatment, mononuclear cells are obtained from HLA-matched healthy donors or the patient and expanded in vitro in the presence of JCV or BK polyomavirus antigenic peptides (both viruses share several immunogenic peptides). Transfer of in vitro stimulated T cells allows the reconstitution of a pool of anti-JCV T cells with cytotoxic capacities.

**Conclusion**

PML is an interesting model to illustrate how understanding a pathology’s underlying immune mechanisms may lead to the design of innovative therapeutic strategies. Although these strategies offer new perspectives for the treatment of PML, it is not the long-awaited panacea as demonstrated in our patient. Large case series tend to suggest it might be beneficial, especially in patients with a grim prognosis.13-15 Unfortunately, the availability of these treatments is still limited to expert centers. Finally, international controlled clinical trials are needed to ascertain efficacy and safety.

**Acknowledgment**

We would like to thank the patient’s family for their help and RevImmune for providing CYT107 for compassionate use.

**Study Funding**

No targeted funding reported.

**Disclosure**

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

**Publication History**

Received by Neurology October 2, 2022. Accepted in final form May 4, 2023. Submitted and externally peer reviewed. The handling editor was Resident and Fellow Deputy Editor Ariel Lyons-Warren, MD, PhD.

**Appendix Authors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tristan Born, BM</td>
<td>Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data</td>
</tr>
<tr>
<td>Paola Vassallo, MD, PhD</td>
<td>Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content</td>
</tr>
<tr>
<td>Dela Golshayan, MD, PhD</td>
<td>Transplantation Center, Department of Medicine, CHUV Lausanne University Hospital and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content</td>
</tr>
<tr>
<td>Giovanni Di Liberto, MD, PhD</td>
<td>Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content</td>
</tr>
<tr>
<td>Jean-Philippe Brouland, MD</td>
<td>Pathology Department, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and the University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content</td>
</tr>
<tr>
<td>Kristof Egervari, MD, PhD</td>
<td>Service of Clinical Pathology, Diagnostic Department, University Hospitals of Geneva, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data</td>
</tr>
<tr>
<td>Doron Merkler, MD</td>
<td>Service of Clinical Pathology, Diagnostic Department, University Hospitals of Geneva, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data</td>
</tr>
<tr>
<td>Renaud A. Du Pasquier, MD</td>
<td>Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content</td>
</tr>
<tr>
<td>Raphael Bernard-Valnet, MD, PhD</td>
<td>Neurology Service, Department of Clinical Neurosciences, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) and University of Lausanne, Switzerland</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data</td>
</tr>
</tbody>
</table>
References


Bridging the Gap: Immunotherapy in Progressive Multifocal Leukoencephalopathy: A New Hope?
Tristan Born, Paola Vassallo, Dela Golshayan, et al.
*Neurology* 2023;101:e1382-e1386 Published Online before print July 5, 2023
DOI 10.1212/WNL.0000000000207533

This information is current as of July 5, 2023

| Updated Information & Services | including high resolution figures, can be found at: | http://n.neurology.org/content/101/13/e1382.full |
| References | This article cites 15 articles, 0 of which you can access for free at: | http://n.neurology.org/content/101/13/e1382.full#ref-list-1 |
| Subspecialty Collections | This article, along with others on similar topics, appears in the following collection(s): |  |
| Amyotrophic lateral sclerosis | http://n.neurology.org/cgi/collection/amyotrophic_lateral_sclerosis_ |  |
| Palliative care | http://n.neurology.org/cgi/collection/palliative_care |  |
| Permissions & Licensing | Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: | http://www.neurology.org/about/about_the_journal#permissions |
| Reprints | Information about ordering reprints can be found online: | http://n.neurology.org/subscribers/advertise |