Drug-induced progressive multifocal leukoencephalopathy: Rare but serious

Carly Rainey, PharmD, BCPS, and Dillon Perryman, PharmD

Christopher Thomas, PharmD, BCPS, BCPP
Department Editor

Mr. P, age 67, presents to the clinic with vision changes and memory loss following a fall in his home due to limb weakness. Six years ago, his care team diagnosed him with rheumatoid arthritis (RA). Mr. P's current medication regimen includes methotrexate 20 mg once weekly and etanercept 50 mg once weekly, and he has been stable on this plan for 3 years. Mr. P also was recently diagnosed with major depressive disorder (MDD), but has not yet started treatment. Following a complete workup, an MRI of Mr. P's brain revealed white matter demyelination. Due to these findings, he is scheduled for a brain biopsy, which confirms a diagnosis of progressive multifocal leukoencephalopathy (PML).

PML is a demyelinating disease of the central nervous system caused by the John Cunningham virus (JCV), or *JC polyomavirus*, named for the first patient identified to have contracted the virus.[1] Asymptomatic infection of JCV often occurs in childhood, and antibodies are found in ≤70% of healthy adults. In most individuals, JCV remains latent in the kidneys and lymphoid organs, but immunosuppression can cause it to reactivate.[2]

JCV infects oligodendrocytes, astrocytes, and neurons, which results in white matter demyelination. Due to this demyelination, individuals can experience visual field defects, speech disturbances, ataxia, paresthesia, and cognitive impairments.[2] Limb weakness presents in 60% of patients with PML, visual disturbances in 20%, and gait disturbances in 65%.[3] Progression of these symptoms can lead to a more severe clinical presentation, including focal seizures in ≤10% of patients, and the mortality rate is 30% to 50%.[3] Patients with comorbid HIV have a mortality rate ≤90%.[2]

Currently, there are no biomarkers that can identify PML in its early stages. A PML diagnosis is typically based on the patient's clinical presentation, radiological imaging, and detection of JCV DNA. A brain biopsy is the gold standard for PML diagnosis.[1]

Practice Points

- **Drug-induced progressive multifocal leukoencephalopathy** (PML) most commonly **arises from immune system weakening**, which can be caused by certain medications.
- Consider a PML diagnosis when **neurologic symptoms and visual field changes occur in high-risk patients** (eg, HIV, immunosuppressive therapy).
- **Discontinuing the offending agent is the primary recommended therapy**; agents that increase immune response are adjunctive options.
- Treatment may include **5HT2A receptor antagonists**.

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)

Dr. Rainey is a PGY-2 Psychiatric Pharmacy Resident, Chillicothe VA Medical Center, Chillicothe, Ohio. Dr. Perryman is a PGY-1 Pharmacy Resident, Chillicothe VA Medical Center, Chillicothe, Ohio.

Disclosures
The contents of this article do not represent the views of the US Department of Veterans Affairs or the US Government. This material is the result of work supported with resources and the use of facilities at the Chillicothe VA Medical Center in Chillicothe, Ohio. The case presented in this article is fictional and does not represent a specific case or person(s). The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0280

Table

Medications that can weaken the immune system

Class	Medication(s)
Oral glucocorticoids	All
Monoclonal antibodies	Abatacept, adalimumab, alemtuzumab, basiliximab, belimumab, bevacizumab, brentuximab vedotin, cetuximab, etanercept, ibritumomab tiuxetan, infliximab, muromonab-CD3, natalizumab, obinutuzumab
Alkylating agents	Cyclophosphamide, dacarbazine
Purine analogs	Azathioprine, cladribine, fludarabine, nelarabine
Antimetabolites	Methotrexate
Immunosuppressants	Cyclosporine, mitoxantrone, mycophenolate mofetil, tacrolimus
Others	Dimethyl fumarate, fingolimod, vincristine

Interestingly, data suggest that glial cells harboring JCV in the brain express receptors for serotonin and dopamine.[4] Researchers pinpointed 5HT2A receptors as JCV entry points into cells, and theorized that medications competing for binding, such as certain psychotropic agents, might decrease JCV entry. Cells lacking the 5HT2A receptor have shown immunity to JCV infection and the ability of cells to be infected was restored through transfection of 5HT2A receptors.[4]

Immunosuppressant medications can cause PML

PML was initially seen in individuals with conditions that cause immunosuppression, such as malignancies and HIV. However, "drug-induced PML" refers to cases in which drug-induced immunosuppression creates an environment that allows JCV to reactivate and disseminate back into the CNS.[4] It is important to emphasize that drug-induced PML is a very rare effect of certain immunosuppressant medications. Medications that can weaken the immune system include glucocorticoids, monoclonal antibodies, alkylating agents, purine analogues, antimetabolites, and immunosuppressants (***Table***).[1]

These medications are used to treat conditions such as multiple sclerosis, RA, psoriatic arthritis, and lupus. Although drug-induced PML can result from the use of any of these agents, the highest incidence (1%) is found with natalizumab. Rates of incidence with other agents are either unknown or as low as .002%.[1] Evidence suggests that the risk for PML increases with the duration of therapy.[5]

Management: Stop the offending agent, restore immune function

Specific pharmacologic treatments for PML are lacking. Management of drug-induced PML starts with discontinuing the offending agent. Restoring immune function has been found to be the most effective approach to treat PML.[3] Restoration is possible through interleukin-2 (IL-2), IL-7, and T-cell infusions. Other treatment options are theoretical and include the development of a JCV vaccine to stimulate host response, plasma exchange to remove the medication from the host, and antiviral therapy targeting JCV replication. Diclofenac, isotretinoin, and mefloquine can inhibit JCV replication.[3]

Based on the theory that JCV requires 5HT2A receptors for entry into cells, researchers have studied medications that block this receptor as a treatment for PML. The first-generation antipsychotic chlorpromazine did not show benefit when combined with cidofovir, a replication inhibitor.[3] Antipsychotics agents such as ziprasidone and olanzapine have shown in vitro inhibition of JCV, while risperidone

Clinical Point

Although very rare, certain medications used to treat MS, RA, psoriatic arthritis, and lupus can cause PML

Discuss this article at www.facebook.com/MDedgePsychiatry

Clinical Point

Second-generation antipsychotics and mirtazapine might be beneficial for treating drug-induced PML

Related Resources

- Castle D, Robertson NP. Treatment of progressive multifocal leukoencephalopathy. J Neurol. 2019;266(10):2587-2589. doi:10.1007/s00415-019-09501-y

Drug Brand Names

Abatacept • Orencia
Adalimumab • Humira
Alemtuzumab • Campath
Azathioprine • Azasan, Imuran
Basiliximab • Simulect
Belimumab • Benlysta
Bevacizumab • Avastin
Brentuximab vedotin • Adcetris
Cetuximab • Erbitux
Chlorpromazine • Thorazine, Largactil
Cidofovir • Vistide
Cladribine • Mavenclad
Cyclophosphamide • Cytoxan
Cyclosporine • Gengraf, Neoral
Dacarbazine • DTIC-Dome
Diclofenac • Cambia, Zorvolex
Dimethyl fumarate • Tecfidera
Etanercept • Enbrel
Fingolimod • Gilenya
Fludarabine • Fludara
Hydroxychloroquine • Plaquenil
Ibritumomab tiuxetan • Zevalin
Infliximab • Avsola, Inflectra
Isotretinoin • Absorica, Claravis
Mefloquine • Lariam
Methotrexate • Rheumatrex, Trexall
Mirtazapine • Remeron
Mitoxantrone • Novantrone
Muromonab-CD3 • Orthoclone OKT3
Mycophenolate mofetil • CellCept
Natalizumab • Tysabri
Nelarabine • Arranon
Obinutuzumab • Gazyva
Olanzapine • Zyprexa
Risperidone • Risperdal
Tacrolimus • Prograf
Vincristine • Vincasar PFS
Ziprasidone • Geodon

has mixed results, with 1 trial failing to find a difference on JCV in fetal glial cells.[3] Second-generation antipsychotics may be the preferred option due to more potent antagonism of the 5HT2A receptors and fewer adverse effects compared to agents such as chlorpromazine.[4] The antidepressant mirtazapine has shown to have promising results, with evidence indicating that earlier initiation is more beneficial.[3] Overall, data involving the use of medications that act on the 5HT2A receptor are mixed. Recent data suggest that JCV might enter cells independent of 5HT2A receptors; however, more research in this area is needed.[2]

The best strategy for treating drug-induced PML has not yet been determined. While combination therapy is thought to be more successful than monotherapy, ultimately, it depends on the patient's immune response. If a psychotropic medication is chosen as adjunct treatment for drug-induced PML, it is prudent to assess the patient's entire clinical picture to determine the specific indication for therapy (ie, treating symptomatology or drug-induced PML).

CASE CONTINUED

Following diagnosis, Mr. P is provided supportive therapy, and his care team discontinues methotrexate and etanercept. Although data are mixed on the efficacy of medications that work on 5HT2A receptors, because Mr. P was recently diagnosed with MDD, he is started on mirtazapine 15 mg/d at night in an attempt to manage both MDD and PML. It is possible that his depressive symptoms developed as a result of drug-induced PML rather than major depressive disorder. Discontinuing methotrexate and etanercept stabilizes Mr. P's PML symptoms but leads to an exacerbation of his RA symptoms. Mr. P is initiated on hydroxychloroquine 400 mg/d for RA management. At a follow-up appointment 4 weeks later, Mr. P reports his sleep, concentration, and overall depressive symptoms have improved. He requests to continue taking mirtazapine.

References

1. Yukitake M. Drug-induced progressive multifocal leukoencephalopathy in multiple sclerosis: a comprehensive review. Clin Exp Neuroimmunol. 2018;9(1):37-47. doi:10.1111/cen3.12440
2. Alstadhaug KB, Myhr KM, Rinaldo CH. Progressive multifocal leukoencephalopathy. Tidsskr Nor Laegeforen. 2017;137(23-24):10.4045/tidsskr.16.1092. doi:10.4045/tidsskr.16.1092
3. Williamson EML, Berger JR. Diagnosis and treatment of progressive multifocal leukoencephalopathy associated with multiple sclerosis therapies. Neurotherapeutics. 2017;14(4):961-973. doi:10.1007/s13311-017-0570-7
4. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone, risperidone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. Med Hypotheses. 2005;65(3):585-586.
5. Vinhas de Souza M, Keller-Stanislawski B, Blake K, et al. Drug-induced PML: a global agenda for a global challenge. Clin Pharmacol Ther. 2012;91(4):747-750. doi:10.1038/clpt.2012.4