# *Progressive Multifocal Leukoencephalopathy in Chronic Lymphocytic Leukemia During Venetoclax Obinutuzumab Therapy: A Rare but Fatal Complication*

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Progressive multifocal leukoencephalopathy (PML) is a rare and potentially fatal demyelinating disease caused by reactivation of John Cunningham (JC) polyomavirus in immunocompromised patients. It has been described mainly in patients with hematological malignancies and following therapies associated with profound immune dysfunction, particularly anti-CD20 monoclonal antibodies [1,2].

Chronic lymphocytic leukemia (CLL) itself is associated with significant immune dysfunction, which may be further exacerbated by targeted therapies. Venetoclax, a BCL-2 inhibitor, and obinutuzumab, an anti-CD20 monoclonal antibody, are an established fixed-duration combination for previously untreated CLL, but their use may contribute to clinically significant immunosuppression and infectious complications [3].

# Case presentation

- A 76-year-old man was diagnosed with chronic lymphocytic leukemia in 2019. At diagnosis, the disease was classified as Binet stage A, with deletion 11q and unmutated IGHV. Given the absence of treatment criteria, the patient was initially managed with active surveillance.
- In 2024, the patient developed progressive disease characterized by worsening anemia, marked lymphocytosis, and generalized lymphadenopathy, leading to progression to Binet stage C. Treatment with the combination of venetoclax and obinutuzumab was initiated.
- Within several weeks of treatment initiation, the patient developed progressive neurological symptoms. The initial manifestations included cognitive impairment, gait instability, and visual disturbances. The neurological condition progressively deteriorated, raising concern for an underlying central nervous system process.
- Brain magnetic resonance imaging (MRI) revealed multifocal white-matter abnormalities, predominantly hyperintense on T2/FLAIR sequences, without significant contrast enhancement. The distribution and appearance of the lesions were highly suggestive of a demyelinating process, raising suspicion for PML in the context of the patient's underlying CLL and recent immunosuppressive therapy.
- Cerebrospinal fluid (CSF) analysis was subsequently performed. Although routine CSF investigations were not remarkable, polymerase chain reaction (PCR) testing detected JC virus DNA, confirming the diagnosis of progressive multifocal leukoencephalopathy.
- Venetoclax and obinutuzumab were immediately discontinued. Supportive treatment, including intravenous immunoglobulin replacement, was initiated in an attempt to improve immune function. Despite these measures, the patient's neurological status continued to deteriorate, resulting in severe neurological disability.

**DISCUSSION** PML is a severe opportunistic infection caused by reactivation of JC polyomavirus in the central nervous system. The virus is widespread in the general population and remains latent in most immunocompetent individuals. In the setting of impaired cellular immunity, JC virus can reactivate, infect oligodendrocytes, and produce progressive demyelination [1,2].

CLL represents a particularly vulnerable setting for opportunistic infections. Even before treatment, patients may have impaired humoral and cellular immunity, including hypogammaglobulinemia, dysfunctional T-cell responses, and impaired innate immune function. These abnormalities can be further aggravated by treatment-related immunosuppression.

- Obinutuzumab is a type II anti-CD20 monoclonal antibody that produces profound and prolonged B-cell depletion. Although highly effective in CLL, anti-CD20 therapy has been associated with opportunistic infections, including rare cases of PML [2,4].
- Venetoclax selectively inhibits the anti-apoptotic protein BCL-2 and induces apoptosis of CLL cells. The combination of venetoclax with obinutuzumab has demonstrated substantial efficacy in previously untreated CLL. In the CLL14 trial, the combination significantly improved progression-free survival compared with chlorambucil plus obinutuzumab. However, grade 3–4 neutropenia occurred in 52.8% of patients and grade 3–4 infections in 17.5%, illustrating the potential infectious burden associated with this regimen [3]. The precise contribution of venetoclax to PML risk remains uncertain. Unlike anti-CD20 therapy, venetoclax is not classically recognized as a direct cause of PML. However, its use may contribute to cumulative immune dysfunction, particularly in patients with advanced CLL, previous therapies, cytopenias, or pre-existing immune impairment. The association between obinutuzumab and PML has been documented in the literature. A published case report described PML in a patient with CLL receiving obinutuzumab, highlighting the potential risk associated with profound B-cell depletion [4]. More recently, a 2025 case report described PML following front-line obinutuzumab and venetoclax in a patient with CLL. The patient developed neurological symptoms shortly after treatment initiation, had JC virus detected in CSF, and subsequently experienced rapid neurological deterioration despite discontinuation of therapy and intravenous immunoglobulin administration [5]. These observations are particularly relevant to our patient, whose neurological symptoms developed shortly after initiation of the same therapeutic combination. Although causality cannot be definitively attributed to either agent individually, the combination of underlying CLL-associated immune dysfunction, anti-CD20-mediated B-cell depletion, and BCL-2 inhibition may have contributed to an immunological environment permissive for JC virus reactivation. The clinical presentation of PML is variable and may initially be subtle. Cognitive impairment, gait instability, visual disturbances, dysarthria, motor deficits, and coordination abnormalities are among the possible manifestations. In our patient, the initial symptoms were relatively nonspecific and progressively worsened, emphasizing the importance of early neurological assessment in patients receiving targeted therapies.
- MRI is central to the diagnostic evaluation. Typical PML lesions appear as multifocal T2/FLAIR hyperintense white-matter abnormalities, often with little or no mass effect and minimal or absent gadolinium enhancement. In the appropriate clinical context, these findings should prompt immediate investigation for JC virus infection. CSF examination can be deceptively unremarkable. The absence of significant pleocytosis or negative routine microbiological studies does not exclude PML. Detection of JC virus DNA by CSF PCR, together with compatible clinical and radiological findings, is sufficient to establish the diagnosis in most cases and may avoid the need for brain biopsy [1]. Management of PML remains extremely challenging. There is currently no established antiviral treatment with proven efficacy against JC virus
- The main therapeutic strategy is restoration of effective immune function and discontinuation of the causative or immunosuppressive treatment whenever possible [1].
- In our patient, targeted therapy was discontinued and intravenous immunoglobulin was administered. Despite these measures, neurological deterioration continued, highlighting the poor prognosis of PML in patients with hematological malignancies.
- This case also emphasizes the importance of maintaining a high index of suspicion. New neurological symptoms in patients with CLL should not automatically be attributed to age, metabolic abnormalities, vascular disease, or treatment-related toxicity. Progressive cognitive, visual, gait, or motor abnormalities should prompt early MRI and, when appropriate, CSF JC virus PCR testing.
- The recent emergence of PML cases associated with modern CLL therapies suggests that clinicians should remain vigilant even with targeted treatments that are generally considered less immunosuppressive than conventional chemotherapy. Long-term immune dysfunction related to CLL, combined with treatment-induced B-cell depletion and cytopenias, may create a permissive environment for rare opportunistic infections

# CONCLUSION

PML is a rare but potentially devastating complication in patients with CLL receiving targeted therapy. Our case illustrates the occurrence of PML shortly after initiation of venetoclax and obinutuzumab, emphasizing the complex and cumulative nature of treatment-related immune dysfunction. New or progressive neurological symptoms, including cognitive impairment, gait instability, or visual disturbances, should prompt early neurological evaluation and brain MRI. When imaging is suggestive, CSF JC virus PCR should be performed promptly, even when routine CSF findings are unremarkable.

There is currently no established antiviral therapy for PML, and prognosis remains poor once significant neurological deterioration has occurred. Early recognition and discontinuation of immunosuppressive therapy, together with appropriate supportive measures, remain the main therapeutic strategies.

As targeted therapies continue to improve outcomes in CLL, awareness of rare opportunistic infections such as PML remains essential. This case highlights the importance of balancing effective disease control with careful long-term monitoring of immune function and infectious complications.

# References

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