Beneath the Surface: Misdiagnosed PML in a Teclistamab-Treated Multiple Myeloma Patient

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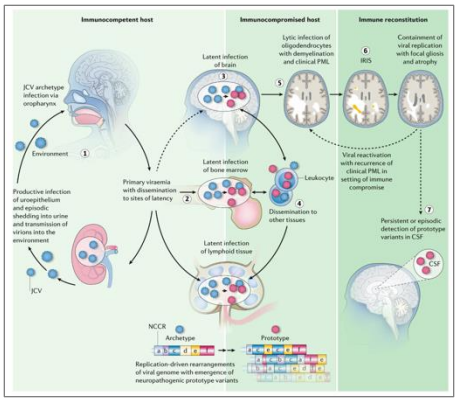
Introduction:

Progressive multifocal leukoencephalopathy (PML) is a rare, debilitating and potentially fatal disease of the Central Nervous System (CNS) resulting from the reactivation of John Cunningham virus (JCV) in individuals with immunodeficiency or undergoing immunosuppressive treatment. While JCV typically establishes a lifelong, asymptomatic latent or persistent infection in the general population; *impaired cellular immune surveillance permits viral reactivation from latent reservoirs*. During this process, JCV may undergo sequential genomic rearrangements, driving intrahost viral evolution. These molecular changes transform an otherwise non-pathogenic virus into a neurotropic pathogen capable of lytically infecting glial cells of the CNS, thereby giving rise to PML *(Fig 1)*.

Teclistamab, a fully humanized IgG4 bispecific antibody targeting B-cell maturation antigen (BCMA), is approved for refractory multiple myeloma. Acting by binding both B-cell maturation antigen (BCMA) on myeloma and CD3 on T-lymphocytes, the drug provokes secondary immunosuppression[2].

We describe a case of PML in a patient treated with Teclistamab, initially misdiagnosed due to its atypical presentation

Figure 1. Pathophysiology of PML[1].



Clinical case:

The patient was a 65-year-old man with a 13-year history of refractory multiple myeloma. He had undergone auto–allogeneic transplantation and received multiple lines of therapy, including carfilzomib, isatuximab, and dexamethasone. The hole clinical history is shown in *Figure 2*.

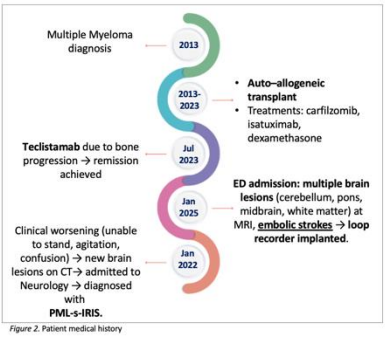


Figure 2. Patient medical history

One year after Teclistamab initiation, the patient presented to our clinic with progressive clinical deterioration, characterized by severe imbalance and **gait instability**.

In the preceding weeks, he had accessed the Emergency Department for the same symptoms and was hospitalized. Documentation from that admission described a brain MRI *(Figure 3)* showing bilateral cerebellar and pontine T2-FLAIR hyperintensities, initially interpreted as **embolic stroke lesions**. Following discharge, his condition further deteriorated, and he was hospitalized again on March 7, 2025. A repeat MRI *(Figure 4)* revealed progression of the lesions, while CSF analysis detected high JC virus titres, confirming the diagnosis of progressive multifocal leukoencephalopathy (PML). Teclistamab was promptly discontinued.

During hospitalization, he developed bilateral interstitial pneumonia with SARS-CoV-2 positivity and persistent neutropenia. Despite supportive and antiviral therapies, neurological deficits persisted. On March 13, 2025, the patient was transferred to the INMI Spallanzani Hospital for **anti-PD-1 immunotherapy** to enhance viral clearance. Unfortunately, his neurological condition did not improve, and he died a few days later.

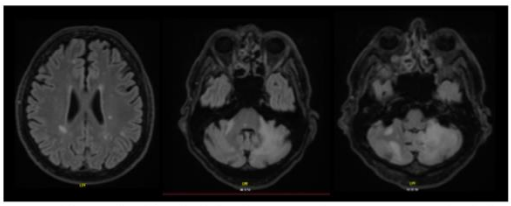


Figure 3. Initial brain MRI showing bilateral cerebellar and pontine T2-FLAIR hyperintensities, misinterpreted as embolic stroke lesions.

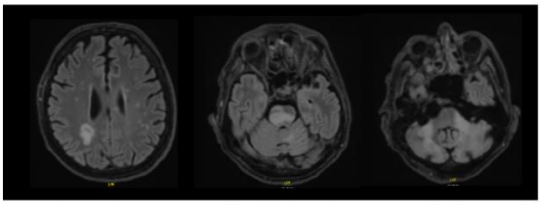


Figure 4. Follow-up MRI demonstrating progression of cerebellar and pontine lesions, consistent with clical deterioration and suggesting PML lesions.

Conclusions:

This case demonstrates how **PML-s-IRIS** can emerge as a severe and often fatal complication of novel biologic therapies such as Teclistamab. The heterogeneous clinical and radiological features may initially mimic other neurological conditions, underscoring the importance of **early suspicion, timely MRI and CSF testing, and close multidisciplinary collaboration**. Despite prompt recognition and escalation of antiviral, antimicrobial, and immunomodulatory treatments, prognosis remained dismal. These findings highlight the **diagnostic complexity** of PML in the era of immunotherapy and the pressing need for more effective and targeted therapeutic approaches.

1. Cortese,I., Reich, D.S & Nath ,A . Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol 17, 37–51 (2021). https://doi.org/10.1038/s41582-020-00437-z
2. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T, Rosinol L, Chari A, Karlin L, Benboubker L, Mateos MV, Bahlis N, Popat R, Besemer B, Martinez-Lopez J, Sidana S, Delforge M, Pei L, Trancucci D, Verona R, Gigigis S, Lin SXW, Olivager Y, Jaffe M, Uhlar C, Stephenson T, Van Rampelbergh R, Banerjee A, Goldberg JD, Kobos R, Krishnan A, Usmani SZ. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022 Aug 11;387(6):495-505. doi: 10.1056/NEJMoa2203478. Epub 2022 Jun 5. PMID: 35661166; PMCID: PMC10587778.

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