When Immunotherapy Turns Against Immunity: Progressive Multifocal Leukoencephalopathy under Teclistamab in Lambda Light Chain Myeloma

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BCMA × CD3 bispecific antibodies, such as teclistamab, have significantly improved treatment options for patients with relapsed or refractory multiple myeloma (RRMM), achieving deep responses even in heavily pretreated patients [1]. However, prolonged BCMA targeting causes depletion of normal plasma cells and can result in profound hypogammaglobulinemia, increasing the risk of serious and opportunistic infections [2].

Progressive multifocal leukoencephalopathy (PML) is a rare but potentially fatal complication caused by reactivation of JC polyomavirus in immunocompromised patients. PML has been reported during teclistamab therapy, including cases occurring after prolonged treatment [3,4].

Case presentation

- **An 83-year-old woman with a history of lambda light-chain multiple myeloma, diagnosed several years previously, was evaluated for relapsed disease. Her disease course was characterized by extensive osteolytic involvement and exposure to multiple previous lines of antimyeloma therapy, resulting in a heavily pretreated clinical setting and substantial cumulative immune dysfunction.**
- **At relapse, treatment with teclistamab was initiated. The patient achieved an initial favorable clinical and biological response, with evidence of effective control of her underlying multiple myeloma.**
- **Several months after treatment initiation, she developed a subtle but progressive neurological syndrome. Initial symptoms consisted of mild gait imbalance and speech difficulties. Over the following weeks, the neurological condition progressively worsened, with marked gait disturbance, dysarthria, and cognitive impairment.**
- **Brain magnetic resonance imaging (MRI) demonstrated multifocal white-matter lesions, predominantly hyperintense on T2-weighted/FLAIR sequences, without significant contrast enhancement. The radiological appearance was considered suggestive of a demyelinating or infectious process rather than central nervous system involvement by multiple myeloma.**
- **Cerebrospinal fluid (CSF) analysis was initially unremarkable, with no significant pleocytosis, sterile cultures, and negative routine viral studies.**
- **Given the progressive neurological deterioration and characteristic MRI findings**
- **, specific JC virus testing was performed. JC virus DNA was detected by CSF polymerase chain reaction (PCR), confirming the diagnosis of progressive multifocal leukoencephalopathy.**

- **Teclistamab was immediately discontinued. The patient received supportive management, including intravenous immunoglobulin replacement and off-label therapeutic approaches aimed at restoring antiviral immune control. Despite these interventions, neurological deterioration continued, reflecting the severe course of PML in the setting of profound immunosuppression**

• DISCUSSION

PML is a rare and potentially fatal demyelinating disease caused by reactivation of JC polyomavirus in oligodendrocytes, predominantly in patients with impaired cellular or combined immunity. Clinical manifestations are variable and may include progressive gait disturbance, dysarthria, cognitive impairment, visual abnormalities, weakness, and coordination disorders [5].

In immunocompromised patients, diagnosis can be challenging because early neurological symptoms may be subtle and nonspecific. In our patient, initial gait imbalance and speech difficulties progressively evolved into a severe neurological syndrome, highlighting the importance of investigating new or unexplained neurological symptoms in patients receiving highly immunosuppressive therapies.

Brain MRI is central to the diagnosis. Typical findings include multifocal T2/FLAIR hyperintense lesions involving the cerebral white matter, generally with limited mass effect and absent or minimal contrast enhancement. The MRI findings in our patient were highly suggestive of a demyelinating process and prompted further investigation for PML. CSF findings may be deceptively unremarkable in PML. The absence of pleocytosis or negative routine viral studies does not exclude the diagnosis. Detection of JC virus DNA by CSF PCR, in the appropriate clinical and radiological context, provides strong diagnostic evidence [5].

The occurrence of PML during BCMA-directed bispecific antibody therapy is particularly concerning. Teclistamab induces profound plasma-cell depletion, affecting both malignant and normal plasma cells, and can therefore result in significant hypogammaglobulinemia and impaired humoral immunity [2]. This effect is compounded by the immune dysfunction associated with multiple myeloma and cumulative exposure to previous therapies.

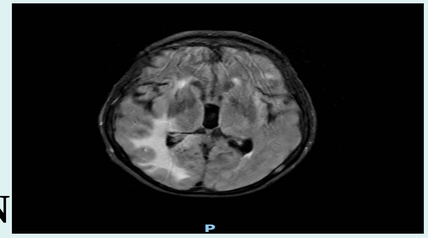
PML has been reported in association with teclistamab. In the MajesTEC-1 experience, a case of grade 4 PML was reported during treatment [1]. Additional cases have subsequently been described, including a case of PML following teclistamab and, more recently, late-onset PML after prolonged exposure [3,4]. These reports suggest that opportunistic viral infections may occur not only during the early phase of treatment but also after prolonged BCMA-directed therapy.

Our case is notable for the patient's advanced age, extensive prior treatment exposure, and delayed onset of neurological manifestations despite an initial favorable response to teclistamab. The initial symptoms could have been attributed to other neurological or treatment-related conditions. However, their progressive nature and the MRI findings prompted appropriate investigation and ultimately led to the diagnosis of PML.

There is currently no established antiviral therapy with proven efficacy for PML. Management primarily relies on restoration of effective immune function and discontinuation of the immunosuppressive treatment whenever possible. In patients receiving teclistamab, discontinuation of treatment is therefore an important component of management following diagnosis.

Intravenous immunoglobulin replacement may be appropriate in patients with severe hypogammaglobulinemia and is an important component of infection prevention and management during BCMA-directed therapy, although its efficacy against established PML remains uncertain [2].

- **This case highlights the importance of systematic immune monitoring during teclistamab treatment. Regular assessment of immunoglobulin levels, appropriate antimicrobial prophylaxis, and early investigation of unexplained neurological symptoms are essential components of supportive care.**
- **As BCMA-directed bispecific antibodies move increasingly into earlier lines of multiple myeloma treatment, patients may be exposed to these therapies for longer periods. The recent description of late-onset PML following teclistamab further emphasizes the need for long-term vigilance for rare opportunistic infections [4**



- **MRI demonstrating Multifocal White matter Abnormalities in a patient with TECLISTAMB-associated Progressive multifocal Leukoencephalopathy,**

• CONCLUSION

PML is a rare but potentially devastating complication that should be considered in patients receiving BCMA-directed bispecific antibodies who develop new or progressive neurological symptoms.

Our case demonstrates that PML may occur several months after initiation of teclistamab despite an initial favorable response of the underlying multiple myeloma. The absence of CSF pleocytosis or negative routine viral studies should not delay specific JC virus PCR testing when clinical and MRI findings are suggestive.

Early neurological assessment, brain MRI, and CSF JC virus PCR testing are essential for establishing the diagnosis. Once PML is confirmed, discontinuation of teclistamab and measures aimed at restoring immune function should be considered.

As BCMA-directed therapies become increasingly integrated into earlier lines of multiple myeloma treatment, clinicians should remain vigilant for rare opportunistic infections and maintain careful monitoring of immune status throughout treatment.

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