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*Case Report*

# Anti-PD1 Treatment of Progressive Multifocal Leucencephalopathy in a Patient with Multiple Myeloma Treated with Anti-Bcma Bispecific Antibodies: A Case Report

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## Abstract

Relapsed/refractory multiple myeloma (RRMM) is still an incurable disease with poor prognosis. Bispecific antibodies, such as Teclistamab, are a new promising option for these patients. However, evidence from clinical trials and real-world experience suggest that they increase the risk of infections, including opportunistic infections like Progressive Multifocal Leukoencephalopathy (PML). To date, only two cases of PML in patients receiving Teclistamab have been reported, both with a fatal outcome.

We present the case of a 51-year-old male with MM refractory to three previous lines of treatment. Eight months after initiating treatment, he was diagnosed of PML after developing neurological symptoms such as diplopia and behavioral changes. Teclistamab was interrupted and treatment with intravenous immunoglobulin (IVIg) and anti-PD1 (pembrolizumab) was initiated. Although there was no improvement in neurological symptoms nor image findings, the patient is still alive 32 months further the diagnosis of PML with slightly clinical improvement of PML and in complete remission with no detectable MRD.

Despite the limited treatment options available, this case shows the importance of early treatment of PML stopping Anti-BCMA therapy and using anti- PD-1 and shows an exceptionally time of survival after diagnosis given the ominous prognosis these patients usually have.

## Keywords

Multiple myeloma, Progressive multifocal leukoencephalopathy, Anti-BCMA bispecific Antibodies, Opportunistic infections.

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## Introduction

Relapsed/refractory multiple myeloma (RRMM) is defined as cases of MM that do not respond to salvage therapies or progress within 60 days after achieving at least a previous minimal response [1]. Despite therapeutic advances over recent decades, it remains an incurable disease. Among the new treatments available are bispecific antibodies (BsAbs) or bispecific T cell engagers (BITEs), as well as CAR-T therapy [2]. A systematic review of the literature

describes response rates ranging from 25% to 100% with anti-BCMA x CD3 bispecific antibodies in RRMM patients, though the response rates vary across different products [3].

Teclistamab is a bispecific antibody that targets the BCMA surface protein. In the phase I-II trial (MAJESTEC-1) [4], teclistamab was administered to RRMM patients, achieving response rates of up to 63% with a median follow-up of 14.1 months [4]. However, regarding infection risk, the trial reported that 80% of patients developed some form of infection, with grade 3-4 cases accounting for up to 55.2% [5]. More recent real-world evidence suggests similar overall response rates and similar incidence for any-grade infection [6]. A comprehensive quantitative assessment of adverse events profile of use of anti-BCMA x CD3 bispecific antibodies in prospective studies shows a rate of 21.63% of grade ≥3 infections [7].

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system caused by reactivation of the JC polyomavirus in patients with significant cellular immunosuppression [8]. It was classically described in patients with HIV/AIDS and in patients with hematological malignancies [9]. Its definitive diagnosis requires histopathological demonstration of virus infection via brain biopsy. However, the diagnosis can also be established using clinical, radiological, and microbiological findings, including positive PCR for JC virus in cerebrospinal fluid [10].

Although rare, PML has previously been described in MM patients. Two systematic reviews of the literature [11,12] identified a total of 33 published cases of PML in MM patients from 1965 to 2023. In a traditional literature search conducted by the authors during the period 2023–2026, eight additional cases [13-20] were identified. To date, only two previous cases of PML in patients treated with teclistamab have been reported in the literature [5,13]. In addition, three other cases of PML have been described in patients treated with anti-BCMA x CD3 and/or anti-GPRC5D x CD3 bispecific antibodies [18-20]. The prognosis of hematological patients who develop PML due to JC virus reactivation remains extremely poor, with a mortality rate of 90% within the first two months after diagnosis [21]. Treatment involves minimizing iatrogenic immunosuppression and restoring T-cell immunity as much as possible [22].

In the present article, we present a case of confirmed PML in a patient treatment with Teclistamab successfully treated with anti-PD1 therapy and IVIg.

## Case Report

We present the case of a 51-year-old male with light-chain lambda RRMM refractory to three previous lines of treatment, diagnosed eight year prior to presentation of the PML. Regarding previous medical diseases, he was an active smoker with hypercholesterolemia without other significant conditions. He was an active individual with no cognitive impairment before the diagnosis of PML.

He was diagnosed after study of generalized bone pain and muscle cramps with detection of Bence-Jones proteinuria in urine. With regard to MM biological characterization, only the t(11:14) translocation was detected. He began treatment with VRD (Velcade/Bortezomid-Revlimid/Lenalidomide-dexamethasone) for six cycles, followed by autologous stem-cell transplantation (SCT) and maintenance with Rd (Revlimid/lenalidomide-dexamethasone). Amidst maintenance treatment he was diagnosed of MM relapse five years past autologous SCT, with generalized bone pain and multiple bone lesions in image studies, for which he started a second line treatment with DVd (Daratumumab-Velcade/Bortezomib-dexamethasone) scheme for eight cycles. Eight months later, a PET-TC scan revealed generalized progression of bone lesions. Thus, treatment with anti-BCMA bispecific antibody (Teclistamab) under compassionate-use was initiated as a third line of treatment, with no early adverse effects reported related to teclistamab administration. However, the patient developed secondary hypogammaglobulinemia due to treatment, and therefore prophylactic use of IVIg was initiated. The patient achieved complete remission with undetectable minimal residual disease at the level of $10^{-5}$, which persists to this day.

Eight months after starting teclistamab, the patient developed subacute neurological symptoms, mainly horizontal diplopia at the extremes of gaze. The patient was evaluated by an ophthalmologist, who recommended completing the workup with a brain MRI. Additionally, the patient began experiencing insidious behavioral changes, including episodes of anger and aggression toward family members.

During an initial outpatient evaluation, the patient exhibited a cachectic state with an ECOG performance status of 2, although the rest of physical examination findings were unremarkable. Laboratory tests at symptom onset revealed no significant abnormalities: complete blood count was within normal limits, with no lymphopenia nor elevation of acute phase reactants, and renal and hepatic function tests showed no alterations. Immunoglobulin levels were found to be decreased at diagnosis of PML (IgG 330 mg/dl). An analysis of lymphocytic subpopulations revealed a slight decrease in CD3+CD4+ lymphocytes count with an inversion of CD4+/CD8+ ratio (0.44).

Brain MRI revealed parenchymal involvement with predominantly bilateral white matter lesions in supra- and infratentorial regions, findings that were suggestive of PML (Figure 1). A lumbar puncture was performed, ruling out MM infiltration by flow cytometry. However, the PCR test for JC virus was positive, while other microbiological tests were negative. Hence, PML was diagnosed.

Following the PML diagnosis, teclistamab was immediately discontinued to restore cellular immunity to the possible extent. Therefore, initially a "wait and see" approach was adopted. However, the patient experienced worsening behavioral symptoms in subsequent months, including episodes of aggression and disorientation, while diplopia remained stable without additional motor focality.

Eventually, the worsening behavioral disturbances led to the need of hospital admission and initiation of specific treatment of the infection with pembrolizumab (200 mg IV) and a single 30 g dose of intravenous immunoglobulin (IVIg). During hospitalization, the patient's neurological state progressively deteriorated, with symptoms of posturing, environmental disconnection, incoherent speech, and exacerbated behavioral disturbances. A follow-up MRI showed radiological progression with worsening of demyelinating lesions, potentially suggesting immune reconstitution inflammatory

syndrome (IRIS). Two additional doses of pembrolizumab (200 mg IV) were administered during hospitalization, and two weeks after the neurological symptoms stabilized.

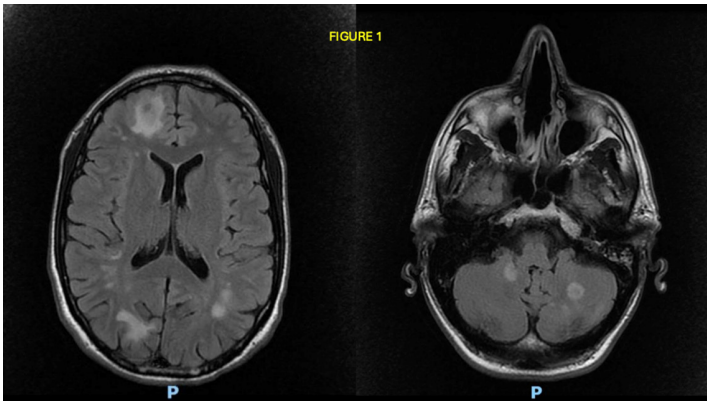


**Figure 1:** Brain MRI (T2/FLAIR, contrast-enhanced) at diagnosis demonstrating bilateral, asymmetrical parenchymal lesions predominantly involving the white matter, with both supratentorial and infratentorial distribution. Findings are consistent with progressive multifocal leukoencephalopathy (PML).

Eventually, the patient was discharged with outpatient follow-up and continued monthly immunoglobulin replacement therapy for 18 months until immunoglobulin levels recovery. At the time of this case report (32 months after PML diagnosis), the patient remains alive in complete response of its MM, with negative minimal measurable disease and with a clear clinical improvement in the neurological symptoms.

## Discussion

This case illustrates the complex interplay between advanced multiple myeloma (MM) treatment, immune modulation, and opportunistic infections such as progressive multifocal leukoencephalopathy (PML), as T cell immunity also appears to be compromised in MM patients [23]. The development of PML in this patient, despite the absence of significant lymphopenia and in the context of targeted immunotherapy with teclistamab [24], highlights the potential for immune reconstitution to unmask or exacerbate JC virus reactivation.

The patient's course underscores several key points. First, the use of BCMA-targeted bispecific antibodies, while highly effective in achieving MM remission, may carry an underrecognized risk of profound immune dysregulation, especially in heavily pretreated patients [25]. Second, the development of PML occurred after multiple lines of therapy, including autologous stem-cell transplantation, proteasome inhibitors, immunomodulatory drugs, and finally, anti-BCMA therapy, suggesting cumulative immune suppression may contribute to JC virus reactivation [26].

The clinical presentation with neurological symptoms, corroborated by MRI findings and positive JC virus PCR, confirms typical PML pathology. The initial management was conservative, including discontinuation of teclistamab and a "wait-and-see" approach; however, the subsequent worsening of neurological and behavioral symptoms necessitated intervention. The therapeutic strategy incorporated pembrolizumab and IVIg, aiming to restore immune function and control JC virus proliferation. Notably, immune reconstitution appeared to be associated with clinical stabilization and radiological improvement, consistent with observations in other PML cases where immune modulation plays a pivotal role [21,27]. Monoclonal antibodies against PD-1 are widely used in oncology to stimulate antitumor immunity. While evidence is scarce, there are clinical reports of PD-1 inhibitors being used to restore immunity and reverse lymphocyte exhaustion associated with PD-1 overexpression in PML patients [28,29].

Finally, this case further suggests that limited-duration anti-BCMA bispecific antibody therapy can lead to sustained, deep, and durable responses even after stopping treatment [30].

## Conclusions

In conclusion, this case emphasizes the importance of vigilant neurological monitoring in MM patients receiving novel immunotherapies and provides insight into potential management approaches for PML, including immune reconstitution strategies. Further research is needed to better understand the immunological mechanisms underlying JC virus reactivation in this context and to optimize treatment strategies balancing MM control with infectious risk mitigation.

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