Late-onset progressive multifocal leukoencephalopathy after teclistamab in multiple myeloma: extending the timeline of infectious risk

Immunotherapy has become an increasingly central component in the treatment of multiple myeloma (MM), representing one of the most dynamic and rapidly evolving areas of clinical research. Among the novel strategies, two main approaches have emerged: chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies targeting plasma cell-associated antigens such as BCMA.[1]

The first bispecific antibody targeting BCMA to enter clinical practice was teclistamab, following the encouraging results of the phase I/II MajesTEC-1 trial, which demonstrated deep and durable responses in heavily pre-treated patients with relapsed or refractory MM. However, despite its remarkable efficacy, the profound and prolonged immunosuppression associated with these therapies may increase susceptibility to severe opportunistic infections.[2]

In the MajesTEC-1 trial, up to 79% of patients experienced infections with 55% of grade 3/4, typically occurring early during the treatment course and the risk of infections with teclistamab remains a major concern, underscoring the importance of prophylactic strategies and prompt treatment interventions.[2,3]

Hypogammaglobulinemia - resulting from both the underlying disease and further compounded by bispecific antibodies that deplete normal plasma cells - contributes to profound immunosuppression and increased vulnerability to opportunistic pathogens.[4]

Beyond the well-recognized early infectious risk associated with bispecific antibodies, accumulating evidence suggests that these agents may induce profound and prolonged impairment of immune reconstitution, particularly through sustained $CD4^+$ T-cell depletion and marked suppression of humoral responses. This persistent immune dysfunction suggests that susceptibility to opportunistic infections may extend well beyond the initial treatment phase, although the true temporal window of risk remains undefined.

In this setting, progressive multifocal leukoencephalopathy (PML) - a rare demyelinating disease of the central nervous system caused by John Cunningham polyomavirus (JC virus) reactivation - has recently emerged as a potential complication. Since 2013, a small but growing number of PML cases have been reported in patients with MM receiving novel immunotherapies, including CAR T-cell therapy, anti-BCMA bispecific antibodies such as teclistamab, and, more recently, anti-GPRC5D bispecific antibodies.[5-8]

Together, these observations raise the possibility of a mechanism shared across T-cell-redirecting therapies, driven by persistent immune dysregulation and impaired viral control, and suggest that opportunistic complications may emerge well beyond the initial treatment phase.

In this context, we describe a case of grade 5 PML occurring in a patient with MM who was in complete remission (CR) and had been receiving teclistamab for 8 months, illustrating an unusually delayed onset and underscoring the need for heightened vigilance during prolonged bispecific antibody therapy.

This case report was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board/ethics committee.

A 44-year-old woman was diagnosed in 2005 with immunoglobulin (Ig)G κ MM with low M-protein secretion, Durie-Salmon stage IIIA. Cytogenetic analysis at diagnosis revealed a biallelic deletion of 1p32. She received induction therapy according to the HOST protocol, followed by high-dose melphalan (MEL200) and autologous stem cell transplantation (ASCT), achieving a partial response. Maintenance therapy with thalidomide was continued for 2 years.

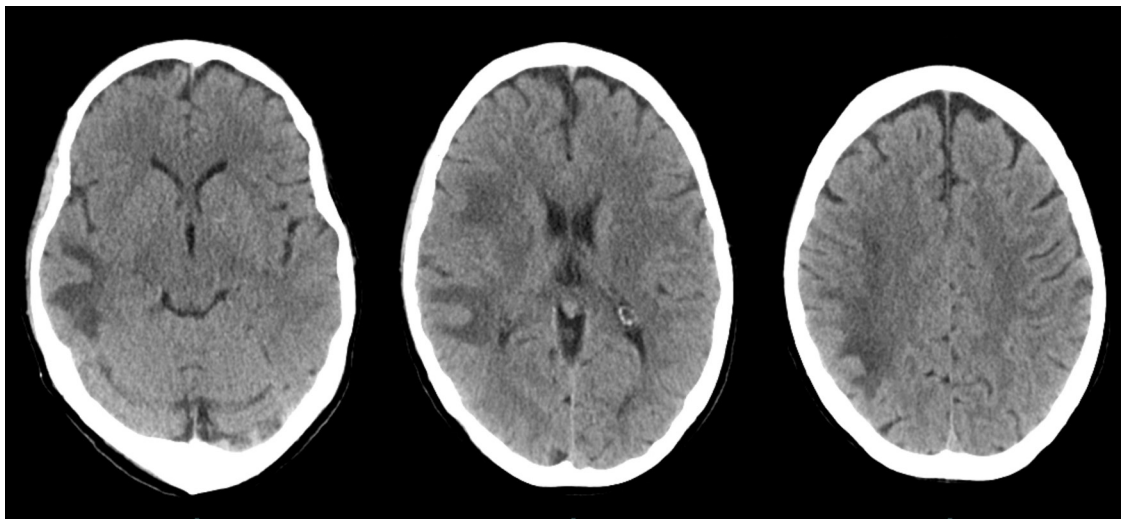

Figure 1. Urgent non-enhanced brain computed tomography. Subcortical multifocal hypodensities are noted in the right cerebral hemisphere, namely in the subcortical lateral temporal and fronto-parietal regions, with minimal effacement of the adjacent sulci; the cortex is apparently intact.

Following disease relapse, she received subsequent lines of therapy including bortezomib–dexamethasone, lenalidomide-dexamethasone, and daratumumab-pomalidomide-dexamethasone and selinexor, with progressively shorter durations of response.

Her disease eventually became penta-refractory, showing resistance to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies. She also developed a pathological acetabular fracture requiring local radiotherapy.

Given her refractory disease status, teclistamab was initiated as sixth-line therapy, leading to a CR, confirmed by negative immunofixation, normalized FLC ratio.

Throughout teclistamab therapy, the patient received regular intravenous immunoglobulin supplementation to maintain serum IgG concentrations within the normal range, in accordance with standard clinical practice.

Treatment had been ongoing for almost 9 months when she developed progressive left-sided hemiparesis.

A cranial computed tomography (CT) scan obtained 5 days after the onset of symptoms revealed a slightly tumefactive large right fronto-temporo-parietal hypodensity, initially interpreted as a space-occupying mass-related edema or a subacute ischemic lesion (Figure 1).

Subsequent brain magnetic resonance imaging demonstrated the absence of a solid mass, though confirming an extensive T2/FLAIR hyperintensity, with corresponding T1 low signal, involving the right temporo-fronto-parietal regions and predominantly affecting the subcortical white matter. The lesion showed no susceptibility changes without obvious enhancement after contrast administration; increased diffusivity was noted within the lesion core, with an edge of reduced diffusion facing the deep white matter (Figure 2). Overall, these radiological features were highly suggestive of PML.

Cerebrospinal fluid (CSF) analysis showed clear appearance, normal protein and glucose levels, and 3 leukocytes (1 polymorphonuclear, 2 mononuclear). Cytology was negative for malignant cells. Multiplex polymerase chain reaction (PCR) for common neurotropic viruses, including Epstein-Barr virus, was negative.

JC virus PCR was positive both in CSF (549 copies/mL) and in plasma (57,700 copies/mL), while Toxoplasma DNA was negative. Lymphocyte subset analysis revealed a CD4 count of 0.26×10^9/L, CD8 count of 1.5×10^9/L, and a CD4/CD8 ratio of 0.17, confirming profound CD4 lymphopenia. Taken together

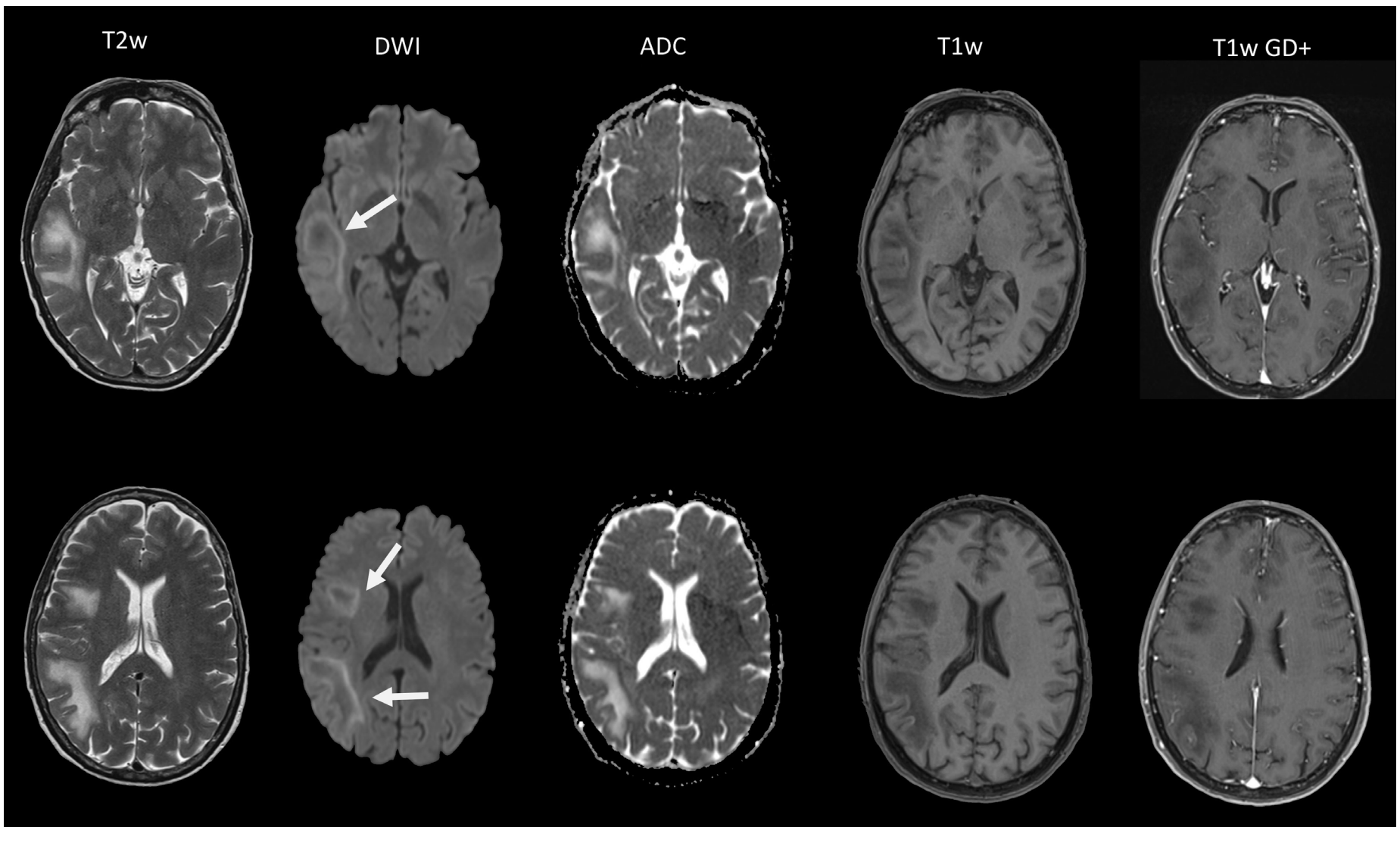

Figure 2. Brain magnetic resonance imaging. Computed tomography hypodense abnormalities correspond to high T2, low T1 signal areas in the subcortical white matter, without enhancement on T1 weighted post-contrast images. On diffusion-weighted imaging , there is a rim of hyperintensity on the lesion edge facing the deep white matter (arrows), whereas apparent diffusion coefficient values on maps are overall increased in the lesion core: this is a hallmark of progressive multifocal leukoencephalopathy.

with the radiologic pattern, these findings were considered highly suggestive of PML, and after multidisciplinary discussion with infectious disease specialists, the process was interpreted as PML occurring in the setting of immune reconstitution inflammatory syndrome. As her neurological condition continued to deteriorate despite supportive measures, the patient was transitioned to best supportive care. This presentation is remarkable for its delayed onset, emerging 8 months after the initiation of teclistamab and at a time when the patient was in CR. While PML has been previously reported in association with teclistamab, this case suggests that vigilance for opportunistic infections may be warranted beyond the early phases of bispecific antibody therapy and highlights the possibility of late immune failure driven by sustained CD4⁺ T-cell suppression despite preserved humoral support.[7,9,10]

Bispecific antibodies such as teclistamab and talquetamab have transformed the management of heavily pre-treated MM, but their activity is accompanied by profound and sustained immune suppression, including CD4⁺ T-cell depletion, impaired B-cell/plasma-cell function and hypogammaglobulinemia. These abnormalities may persist despite hematologic response and create vulnerability to opportunistic viral reactivation. Notably, in our patient, IgG levels were maintained through regular intravenous immunglobulin supplementation, indicating that humoral deficiency alone is insufficient to explain the development of PML and underscoring the importance of cellular immune impairment - particularly sustained CD4⁺ lymphopenia.

Most infections associated with bispecific antibodies occur early during therapy, with a median time to first infection of approximately 1.7 months.[11] In contrast, our case demonstrates that PML can arise as a late complication even in patients with deep remission, suggesting that susceptibility extends long beyond the initial treatment phase and that current monitoring strategies may underestimate late infectious risk.

A small number of PML cases have been reported in MM patients receiving novel T-cell-redirecting therapies; including the present case, five have been identified. These include: (i) a case reported in the MajesTEC-1 trial during teclistamab therapy, with limited immunologic data available;[10] (ii) a separate teclistamab-associated case occurring immediately after the first ramp-up dose;[7] (iii) a case linked to the anti-GPRC5D bispecific antibody approximately 2 months after initiation, despite monthly IVIG supplementation;[12] and (iv) a case reported after anti-BCMA CAR T-cell therapy (ide-cel), after 6 months from CAR infusion.[9] Despite heterogeneous reporting, common features include heavy pre-treatment, persistent cellular immune dysfunction, and inconsistent humoral recovery. Importantly, whereas previous cases predominantly describe early-onset PML, our patient illustrates a markedly delayed presentation, broadening the interval during which clinicians should remain vigilant (Table 1).

Neuroimaging and CSF findings in our patient were diagnostic for PML. These observations reinforce that JC virus PCR testing in CSF should be performed promptly in any MM patient receiving bispecific antibodies who develop new neurological symptoms or unexplained cognitive decline.[13] Enhanced immune monitoring, including serial CD4⁺ T-cell quantification and immunoglobulin levels, may help to identify patients at higher risk.[14] In selected cases, dose spacing or temporary treatment interruption may support partial immune reconstitution, although this strategy war-

Tabel 1. Features of reported progressive multifocal leukoencephalopathy cases in multiple myeloma.

Pt #	MM therapy at time of PML	MM response at PML	Line of therapy	Time from therapy start and PML dx, months	CD4 count at PML, cells/µL	CD8 count at PML, cells/µL	IgG at PML, mg/dL	PML treatments	Outcome/ time to death
1	teclistamab (BiTE, clinical trial)	CR	5	NA	unknown	unknown	258	pembrolizumab (3 doses)	died/75 days
2	observation after ide-cel (with Flu/ Cy conditioning)	sCR	9	6	<35	<45	341	corticosteroids, pembrolizumab (1 dose)	NA
3	teclistamab	PD	7	after 1 ramp-up dose	NA	NA	NA	best supportive care	NA
4	talquetamab	CR	8	2	NA	NA	NA	best supportive care	died/2.5 months
5 (present case)	teclistamab	CR	6	8	<26	<15	806	corticosteroids	died/30 days

CR: complete remission; sCR: strigent CR; dx: diagnosis; IgG: immunoglobulin G; PML: progressive multifocal leukoencephalopathy; PD: progressive disease; Pt: patient; Flu/Cy: fludarabine with cyclophosphamide; MM: multiple myeloma; NA: not available.

rants prospective evaluation.
Although causality cannot be definitively established, the absence of alternative explanations and the profound T-cell lymphopenia observed in our patient is consistent with a permissive role of teclistamab-induced immune dysfunction in enabling delayed JC virus reactivation.
More broadly, this case underscores the need to consider JC virus reactivation as potential late complications of T-cell-redirecting therapies and suggests that current monitoring strategies may be insufficient for patients with persistent or profound immune impairment. Prospective studies are needed to define immunologic and clinical predictors of susceptibility to opportunistic infections in patients receiving bispecific antibodies, with the goal of identifying those who may benefit from enhanced surveillance or modified dosing strategies.

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Disclosures

No conflicts of interest to disclose.

Contributions

DC performed the research, analyzed the data and wrote the manuscript. CD prepared and curated the imaging material. ET, FC, and MLL supervised the study, contributed to data analysis and critically revised the manuscript. All remaining authors were involved in the clinical care of the patient and contributed to data interpretation and critical revision of the manuscript.

Data-sharing statement

The data that support the findings of this case report are available from the corresponding author upon reasonable request.

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