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Progressive multifocal leukoencephalopathy during bispecific antibody therapy in multiple myeloma: from immune dysfunction to early recognition. Comment on: "Progressive multifocal leukoencephalopathy and BK virus-nephropathy with bispecific antibody therapy in multiple myeloma"

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Running head: PML during bispecific antibody therapy.

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The recent study by Siegel et al.[1] provides important insights into the severe immune dysfunction associated with therapy using bispecific antibodies that redirect T cells in multiple myeloma (MM). The authors describe a patient treated sequentially with bispecific antibodies targeting BCMA and GPRC5D, who developed BK virus-associated nephropathy followed by rapidly fatal progressive multifocal leukoencephalopathy (PML). It is important to emphasise that longitudinal analysis of the immune profile revealed impairment of both humoral and cellular immunity, including the loss of JC virus (JCV)-specific CD8+ T-cell responses, which preceded the clinical onset of PML[1]. These findings provide a biological framework for an increasingly recognized clinical concern: PML during prolonged exposure to bispecific antibodies.

PML has historically been regarded as a rare complication of MM and its treatment. Prior to the widespread use of T-cell-redirecting therapies, Koutsavlis identified 16 well-documented cases of PML in MM and suggested that this complication might be underdiagnosed[2]. Subsequently, Hoeynck et al. described six patients with MM who developed PML, including a patient exposed to teclistamab, providing an early signal in the era of BCMA-directed therapies[3]. More recently, individual cases have been reported with both teclistamab and elranatamab, including two patients receiving elranatamab reported by Tomkins et al. and a further elranatamab-associated case described by Çetiner et al[4,5].

This emerging association is now supported by larger contemporary cohorts. Gadoth et al. recently reported five patients who developed PML following treatment with bispecific antibodies; all were receiving a bispecific antibody directed against BCMA at the time of PML diagnosis. The median interval between the start of bispecific antibody therapy and the onset of PML was 12 months (range, 6–24), and all patients had lymphopenia and hypogammaglobulinaemia prior to diagnosis[6]. Importantly, one patient developed PML after only two prior lines of therapy, suggesting that cumulative pretreatment alone may not fully explain susceptibility[6]. Furthermore, Le Henaff et al. identified 14 definite cases of PML among patients with MM exposed to bispecific antibodies, all involving BCMA-targeting agents, with a median exposure of 22 months. Their pharmacovigilance analysis identified a significant disproportionality signal for PML with bispecific antibodies compared with other MM therapies (reporting odds ratio, 17.7; 95% CI, 12.1–26.1)[7]. Although these observations do not allow us to establish a causal link or to estimate the incidence, they reinforce the emerging association between prolonged exposure to the bispecific antibody directed against BCMA and PML.

Our recent multicenter SEIFEM study provides complementary real-world evidence[8]. Among 35 patients with hematologic malignancies diagnosed with PML across 16 Italian centers, seven (20%) had MM and two developed PML after bispecific antibody therapy, including one receiving elranatamab. Overall prognosis was poor, with a median survival from PML diagnosis of 2.17 months and 80% mortality. Importantly, the median interval between neurological symptom onset and PML diagnosis was 28 days (range, 2–110), highlighting the considerable diagnostic challenge posed by this disease[8].

The patient treated with elranatamab represented the upper extreme of this diagnostic interval. This 62-year-old woman had previously received daratumumab, bortezomib, thalidomide and dexamethasone followed by autologous stem-cell transplantation. At relapse, she received

elranatamab and developed motor and speech impairment after 11 months of treatment. Brain magnetic resonance imaging showed a single frontal lesion, and PML was ultimately diagnosed by detection of JCV DNA in cerebrospinal fluid (CSF) 110 days after neurological symptom onset. At diagnosis, neutropenia, lymphopenia and hypogammaglobulinemia were present.

The 11-month exposure in our patient is remarkably consistent with the temporal pattern emerging from recent reports. Gadoth et al. observed a median exposure of 12 months[6], while Chizzoniti et al. recently described late-onset PML after approximately nine months of teclistamab therapy[9]. Collectively, these observations suggest that PML may represent a delayed complication of sustained immune dysfunction rather than an early toxicity of bispecific antibody therapy.

The immunological findings are equally important. Severe hypogammaglobulinaemia is a well-known complication of BCMA-targeted therapy, but the preservation or replacement of immunoglobulins may not fully restore antiviral immune surveillance. Chizzoniti et al. reported cases of PML despite regular immunoglobulin replacement therapy, in a context of marked CD4+ lymphopenia[9]. Similarly, Gadoth et al. demonstrated a reduction in the populations of naïve CD4+ and CD8+ T lymphocytes and a phenotypic shift towards terminally differentiated, activated and exhausted cells[6]. It is interesting to note that JCV/BKV-specific T-cell responses remained detectable in two of the four patients assessed, suggesting that qualitative T-cell dysfunction may be as significant as their quantitative depletion[6]. These observations complement the longitudinal findings of Siegel et al.[1] and support a potential role for sustained cellular immune dysfunction in PML susceptibility.

Early diagnosis is therefore crucial. Neurological symptoms may initially be attributed to cerebrovascular disorders, metabolic abnormalities, treatment-related neurotoxicity or other infections. Furthermore, a negative PCR result for JCV in cerebrospinal fluid does not rule out PML: in the SEIFEM and Gadoth series, some selected patients required a brain biopsy despite a negative cerebrospinal fluid test result[6,8]. New, otherwise unexplained progressive neurological symptoms during bispecific antibody therapy should therefore prompt early brain MRI and CSF JCV testing, with repeat testing or brain biopsy considered when clinical and radiological suspicion persists.

As bispecific antibodies move into earlier treatment lines and exposure becomes increasingly prolonged, PML deserves greater attention as a rare but potentially fatal complication. Current evidence does not justify routine JCV screening, and the absolute risk remains undefined. Nevertheless, the convergence of clinical series, pharmacovigilance data and emerging immunological evidence suggests that duration of exposure, lymphopenia and qualitative T-cell dysfunction warrant prospective investigation as potential risk markers. Increased awareness and timely diagnostic evaluation may currently represent our most effective tools for reducing the devastating consequences of delayed PML recognition.

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