Progressive multifocal leukoencephalopathy and BK virus-nephropathy with bispecific antibody therapy in multiple myeloma

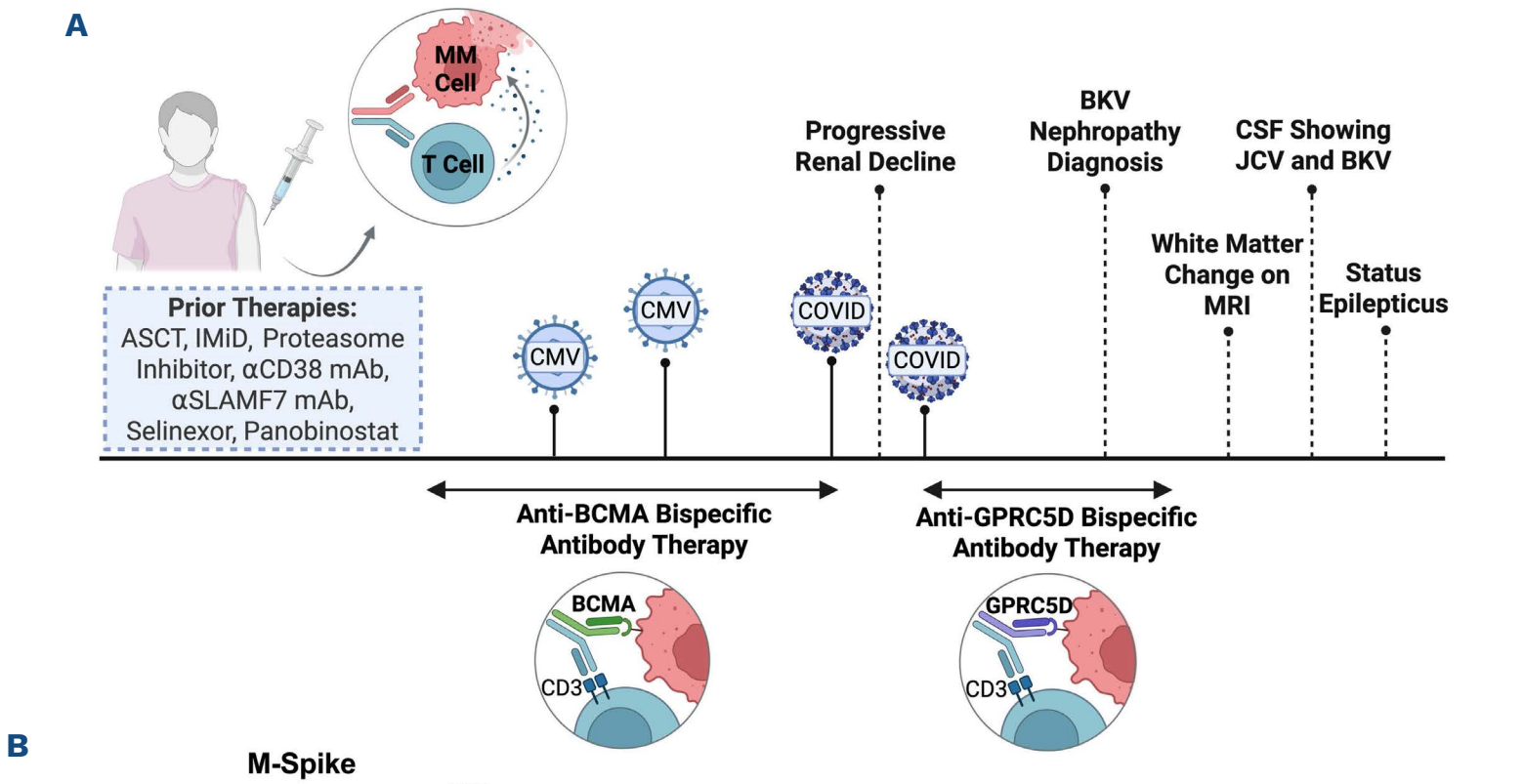
T-cell redirecting therapies have dramatically altered the treatment landscape of multiple myeloma (MM). Bispecific antibodies (BiAb) have been shown to induce deep and durable responses in MM, even in those with heavily pre-treated disease. Despite their efficacy, there is a significant risk of infection, with severe (grade 3 or higher) infectious complications occurring in up to 45% of MM patients treated with BiAb.[1] Here we describe a unique case of a patient with MM treated sequentially with anti-BCMA x CD3 and anti-GPRC5D x CD3 BiAb who developed both renal failure from BK polyomavirus 1 (BKV) associated nephropathy and rapidly fatal neurologic decline due to progressive multifocal leukoencephalopathy (PML), with loss of both humoral and virus-specific cellular immunity, clearly demonstrable by longitudinal multi-modal immunophenotyping and functional assays.

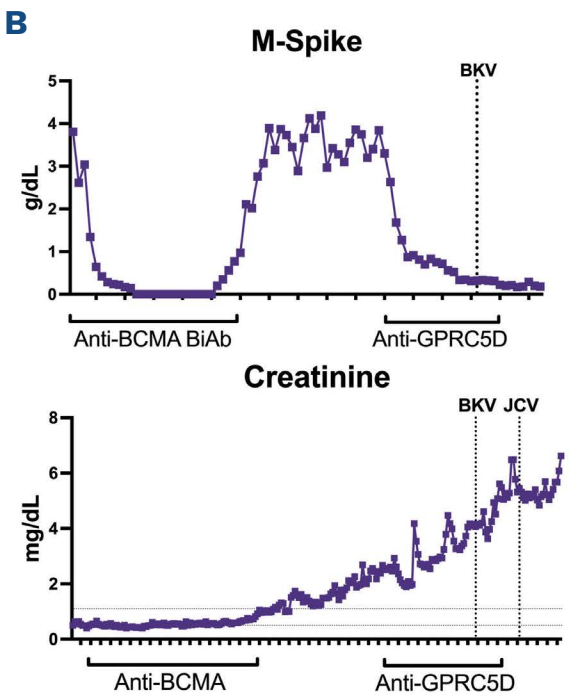
We present a 66-year-old female with heavily treated IgG kappa MM who received an anti-BCMA x CD3 BiAb for salvage therapy after her seventh relapse. She progressed after two years of therapy and shortly thereafter developed progressive renal dysfunction (Figure 1A, B), whose etiology was initially ascribed to MM progression. She was treated with chemotherapy (dexamethasone, cyclophosphamide, etoposide and cisplatin, then bendamustine and bortezomib) and ultimately started on anti-GPRC5D x CD3 BiAb therapy. She responded rapidly to therapy but had persistent decline in renal function and a renal biopsy was performed, which demonstrated BKV-associated nephropathy, an entity more commonly seen in solid organ transplant recipients (Figure 1C). Approximately two months later, she developed progressive decline in mental status, initially with confusion, then ultimately became less responsive, requiring hospitalization. She subsequently required intubation for airway protection, and MRI was notable for new white matter hyperintensities in the temporal and occipital lobes, consistent with PML, a rare and devastating demyelinating disease of the central nervous system caused by the reactivation of the JC polyomavirus 2 (JCV) in the setting of severe immunosuppression (Figure 1D). Plasma showed marked elevation of BKV and JCV by PCR (BKV 9.9 million copies/mL, JCV 15,600 copies/mL) as did the cerebrospinal fluid (BKV 54,700 copies/mL, JCV 120,000 copies/mL), confirming the diagnosis of PML. The patient developed status epilepticus and died shortly thereafter. An autopsy was performed with the family's consent, which confirmed demyelination and viral inclusions in the brain by immunohistochemistry for Simian Virus 40 (SV40) large T antigen (Ag), a key polyomavirus protein involved in viral transformation of host cells (Figure 1E).[2]

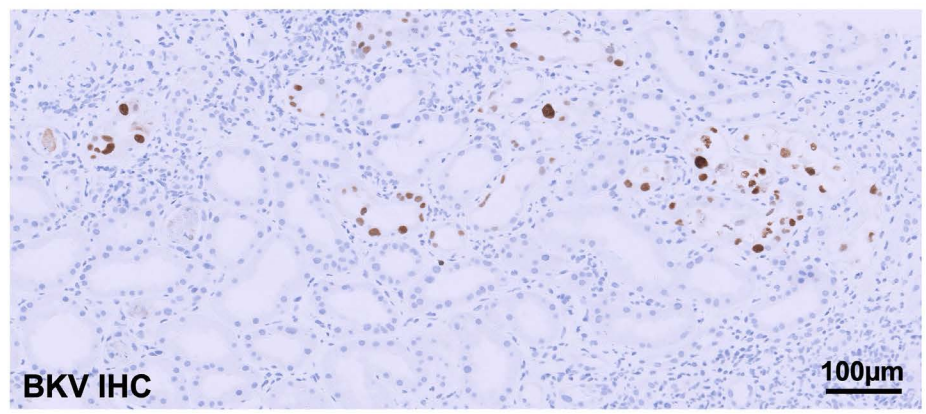
To assay humoral protection against BKV and JCV, we used a multiplexed in-solution protein array (MISPA) platform, which uses a protein-antigen library to evaluate and compare serologies of a large scale of samples to hundreds of Ag simultaneously (Figure 2A).[3] This platform includes the SV40 small t Ag, which shares sequence homology with BKV and JCV.[4] Polyomavirus small t Ag are thought to assist in viral replication via transregulatory activity on promoters transcribed by RNA polymerases II and III.[5] We collected longitudinal serum samples from our patient, under Multiple Myeloma Biorepository IRB Study ID 18-00456 (approval date 04/26/2024), and analyzed five of these samples while on anti-BCMA x CD3 BiAb therapy via the MISPA platform. We compared the antibody levels of our patient to those of healthy controls (N=100). Notably, there was a significant decrease in antibody levels against SV40 small t Ag when compared to healthy controls. Similarly, a decrease in antibody response was also seen to other viral Ag, including various COVID and seasonal coronavirus Ag (Figure 2B). It is interesting to note that the patient's antibody levels remained low despite regular IVIg infusions.

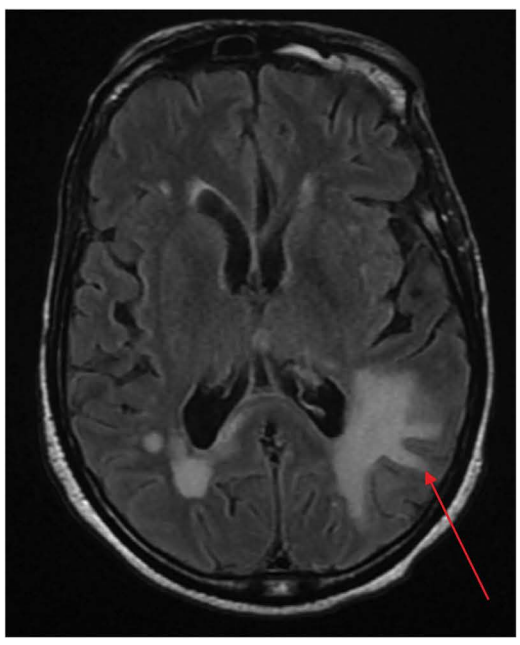
Cellular immunity has been previously described to have a major role in patients with PML or BKV nephropathy, and adequate T-cell immunity is required. Early $CD8^+$ T-cell response is more frequently seen in long-term PML survivors when compared to those with rapidly progressive disease.[6,7] We, therefore, investigated changes in peripheral blood immunophenotypes, as well as T-cell-mediated anti-viral responses, throughout her treatment course. Spectral flow cytometry-based immunophenotyping showed a decrease in subpopulations of $CD4^+$ and $CD8^+$ T cells, NK cells, as well as B cells throughout the treatment course (Figure 3A, B).

To test virus specific T-cell responses, peripheral blood mononuclear cells (PBMC) were stimulated with a peptide pool of cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza, and tetanus (CEFT), JCV small T Ag (ST), and BKV ST Ag peptides. Intracellular cytokine staining was performed to assess cytokine production as previously published by our group.[8] We compared the aggregate cytokine production from $CD8^+$ cells to evaluate changes in T-lymphocyte function (Figure 3C). Across the different peptides, a decrease in $CD8^+$ T-cell recall response was









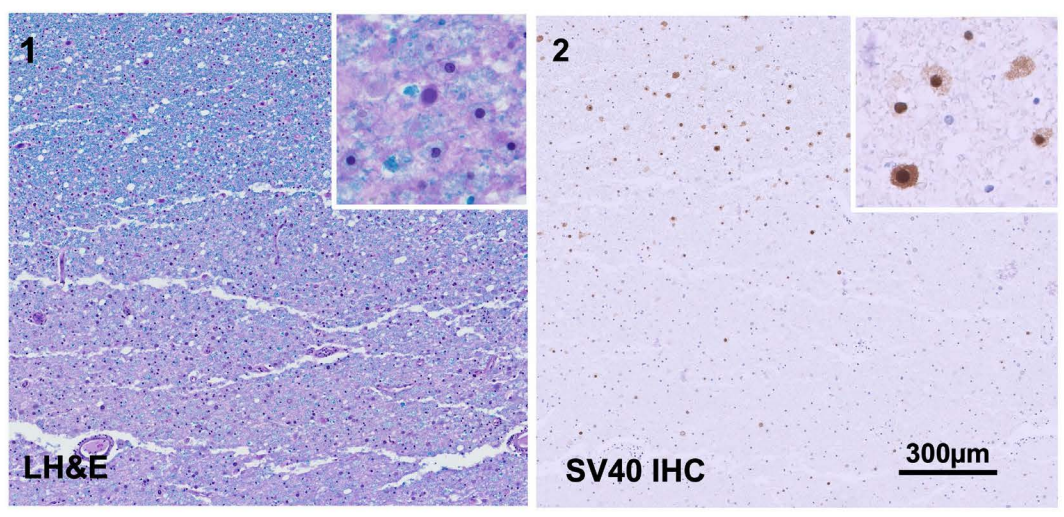


Figure 1. Clinical events. (A) Timeline of multiple myeloma (MM) therapy with notable clinical events. (B) M-spike and creatinine levels throughout the BiAb treatment course. (C) Renal biopsy with immunohistochemistry (IHC) for BK polyomavirus (BKV) showing marked tubulointerstitial mononuclear inflammation and tubular epithelial cells showing positive nuclear staining (magnification 20X). (D) MRI brain showing new white matter hyperintensities in the temporal and occipital lobes (indicated by red arrow). (E) Brain tissue after autopsy. 1. Luxol fast blue-hematoxylin and eosin (LH&E) stain shows a demyelinated lesion characterized

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by pallor of the white matter and numerous foamy macrophages containing phagocytosed myelin debris. Inset highlights individual macrophages with vacuolated cytoplasm in the area of pallor and an abnormal oligodendrocyte nucleus. 2. IHC SV40 large t Ag demonstrates abundant nuclear positivity in infected oligodendrocytes within the lesion, consistent with JC virus infection. Inset shows higher magnification of SV40-positive nuclei.

seen while on anti-BCMA x CD3 BiAb therapy. While on the anti-BCMA x CD3 BiAb, the patient lost recall response to CEFT control prior to a clinically relevant CMV infection; she also lost recall response to BKV prior to the development of renal dysfunction and the eventual diagnosis of BKV nephropathy. There was a loss of $CD8^+$ T-cell response to JCV while on anti-BCMA x CD3 BiAb, which predated clinically relevant PML. While on anti-GPRC5D x CD3 BiAb, there was some recovery of $CD8^+$ T-cell response to both BKV and JCV Ag, but this was either insufficient or too late to control the BKV nephropathy or PML.

Progressive multifocal leukoencephalopathy has rarely been described with the use of anti-BCMA x CD3 BiAb.[1,9] How to identify patients at the greatest risk of such devastating opportunistic infections is less understood. We have previously described a specific immunophenotype in MM patients treated with BCMA-directed therapy that have sub-optimal responses to COVID vaccination.[10] Similarly, in our patient, not only was there a loss of humoral immunity during anti-BCMA x CD3 BiAb therapy, but there was a loss of B cells, T cells, NK cells, and a relative loss of TfH cell subsets as well. During this time, virus-specific T-cell recall function was also compromised. These changes in both humoral and cellular immunity corresponded to the patient's clinical complications and decline. While there was some recovery of these cell types and T-cell recall function while on anti-GPRC5D x CD3 BiAb therapy, the immune response was ineffective in controlling the infections. Even though the patient was receiving monthly IVIg infusions, it did not mitigate this life-threatening infection. Our case highlights the need for prompt recognition of, and possibly even surveillance for, rare infections such as BKV and PML. Timely recognition of BKV may require renal biopsy and PCR testing of blood and urine. Similarly, evaluation of cerebrospinal fluid PCR in the appropriate setting of mental status changes with BiAb therapy may allow for prompt diagnosis of PML. Maintaining a high degree of suspicion for opportunistic infections in patients receiving BiAb therapy is of utmost importance. As described in the literature, infections may arise early on in therapy, with specific BiAb demonstrating a median time to first infection of 1.7 months and documented infections occurring as early as 0 months.[11] Adoption of immune phenotyping to identify patients at the highest risk of infection, and perhaps reducing dosing frequency of BiAb in patients to allow for reconstitution of immune

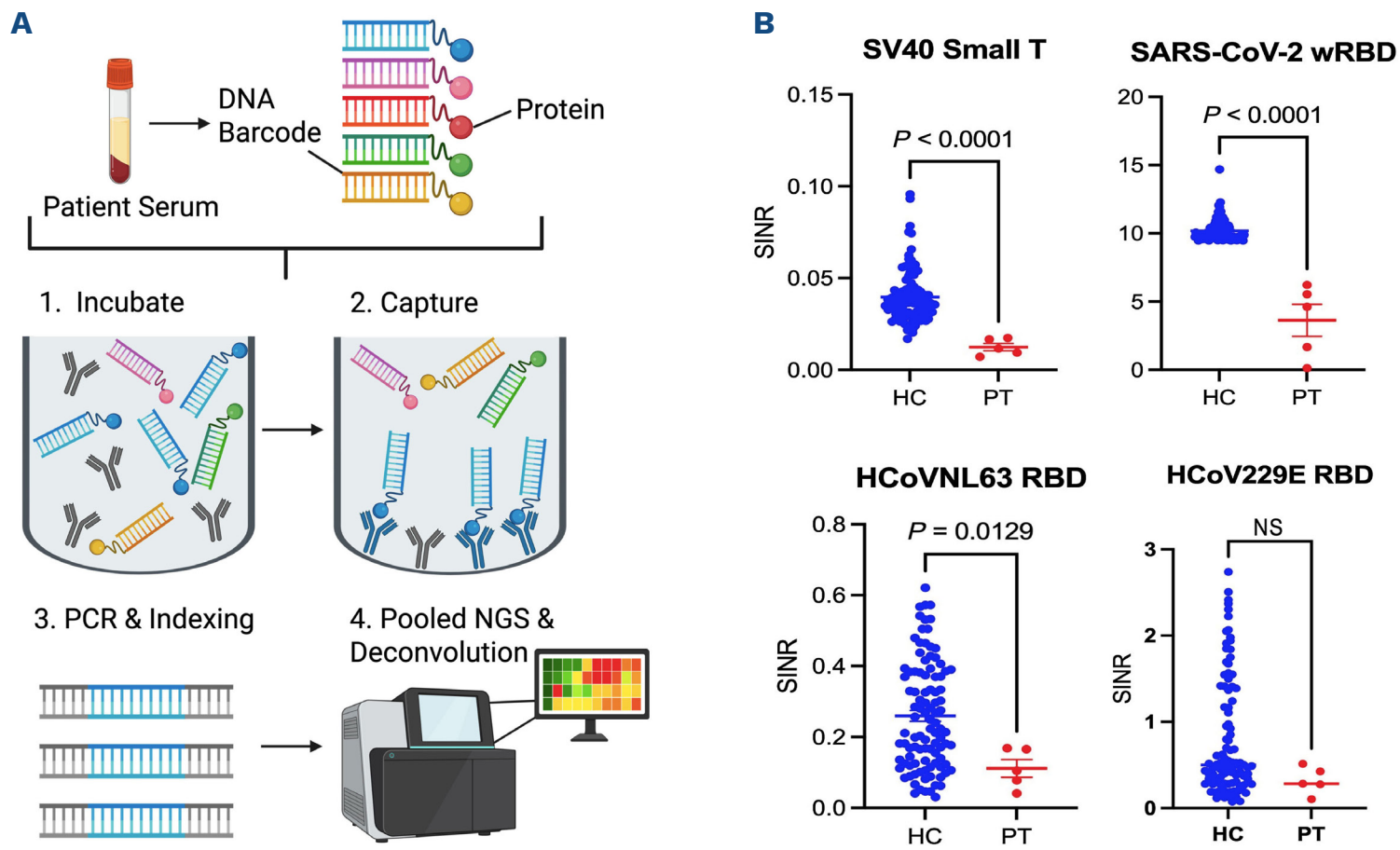

Figure 2. Serological analysis. (A) Schematic workflow of the MISPA platform, showing a protein Ag library linked to a unique DNA barcode that is incubated with a patient sample then antibody-bound Ag are isolated and amplified using PCR with pooled PCR products further evaluated by next-generation sequencing. (B) Case patient (PT) MISPA results compared to those of 100 healthy controls (HC), specifically SV40 small t Ag, a COVID-19 Ag, and two seasonal coronavirus Ag (NS: not significant).

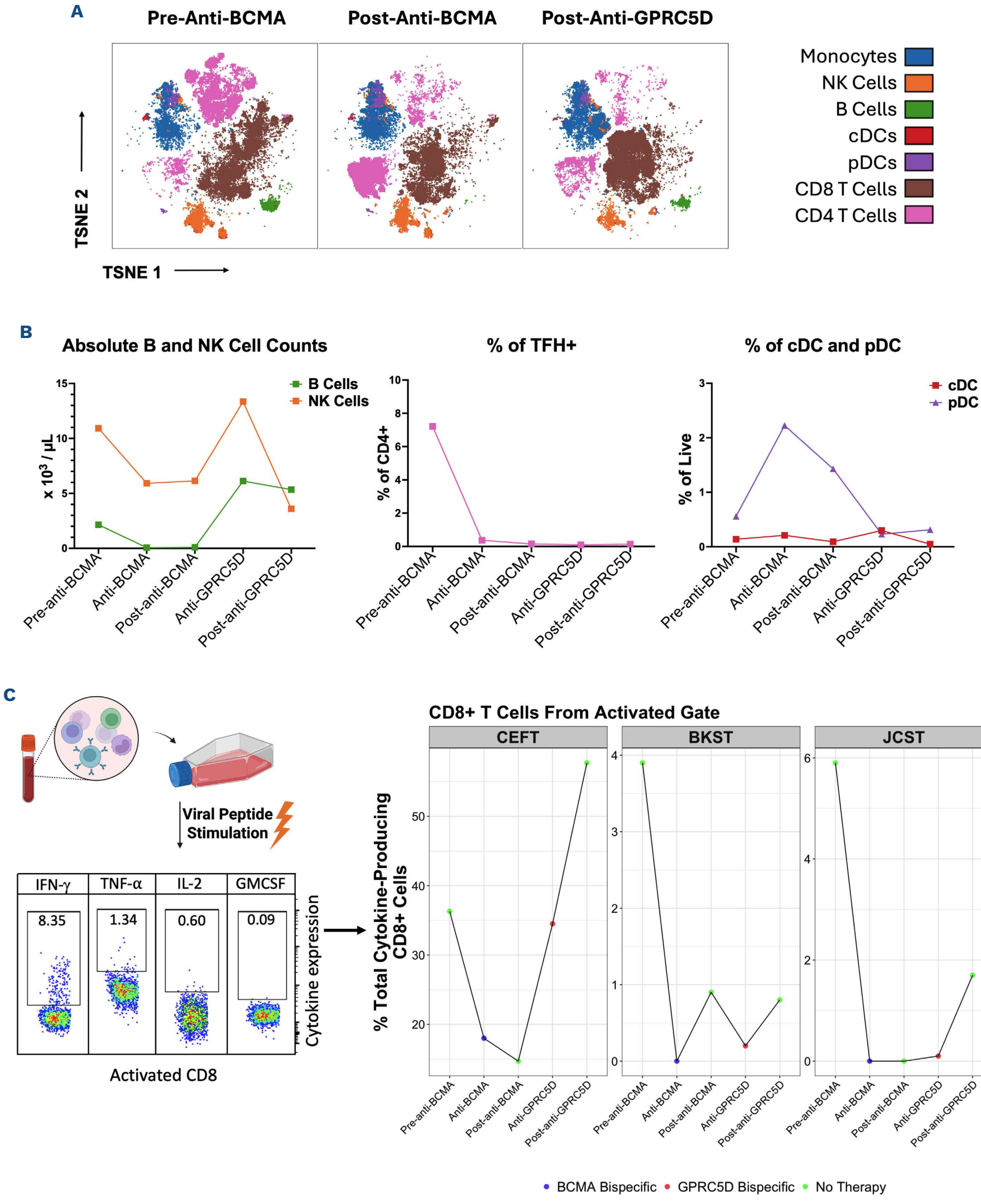

Figure 3. Longitudinal immunophenotyping and functional assays. (A) TSNE plots and (B) scatter plots assessing immunophenotype from peripheral blood patient samples throughout the bispecific antibodies (BiAb) treatment course. (C) Viral-specific T-cell responses assessed after stimulation of patient peripheral blood mononuclear cells with CEFT control, BKV ST Ag, and JCV ST Ag peptides with intracellular cytokine staining performed to assess cytokine production from $CD8^+$ T cells to evaluate T-lymphocyte function. TFH: T follicular helper cells; cDC: conventional dendritic cells; pDC: plasmacytoid dendritic cells.

function, is an important consideration. As some recovery of T-cell recall function was seen with anti-GPRC5D x CD3 as compared to anti-BCMA x CD3 BiAb therapy, sequencing anti-GPRC5D x CD3 BiAb prior to anti-BCMA x CD3 BiAb therapy in these patients may help to mitigate the risk of infection. This case highlights a need to increase awareness of BKV and JCV-associated infections in BiAb-treated patients, and for additional research to identify patients with MM who are more susceptible to severe infections on BiAb therapy.

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Contributions

AS and SR performed research and data analysis, wrote the manuscript, and created the figures; LG and SD edited the manuscript and contributed to data analysis; CG contributed to data analysis; JC, LS, JP, IS and JL contributed to data analysis and contributed to the figures; DV contributed to patient care and reviewed the manuscript; KK reviewed the manuscript and contributed to data collection; SJ contributed to data analysis and reviewed the manuscript; AA and SP supervised the study, analyzed data, and edited the manuscript.

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Illustrations were created in BioRender.

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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