Epstein Barr Virus-specific T lymphocyte response in a case of “accelerated” multiple sclerosis onset

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Background Immune reactivity to viruses, with the associated T and B cell maturation dynamics and innate inflammatory signatures are emerging as interlinked drivers of disease activity and progression in multiple sclerosis (MS). The role of EBV infection has gained centre stage in MS, but how the exposure to EBV influences the immune response in the early phase of the disease is still unclear.

Aims We characterized virus-specific CD4+ T cell reactivity and multi-compartmental immune activation in a young person who presented with a rapid transition from an MRI-negative to an MRI-positive state at the time of MS onset (Fig.1).

Methods High-dimensional flow cytometry was performed on fresh peripheral blood from a newly diagnosed patient with a severe acute onset of multiple sclerosis. Clinical evaluation and neuroimaging were performed at initial presentation and subsequently two or three-month intervals, corresponding to the emergence of new clinical symptoms. The immunological analysis included absolute quantification and characterization of B and T cell subsets, along with functional assessment of innate immune cells. These data were compared with those from a reference cohort of multiple sclerosis patients.

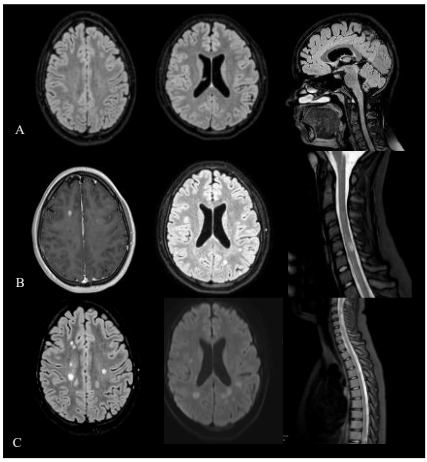

FIG.1. Initial MRI showed no abnormalities (A). Three months later, brain and spinal cord MRI with gadolinium-based contrast revealed multiple enhancing lesions (B). After 210 days (relapse), coinciding with the onset of new clinical symptoms, a gadolinium-enhanced MRI demonstrated marked disease activity (C).

Immunological profiling

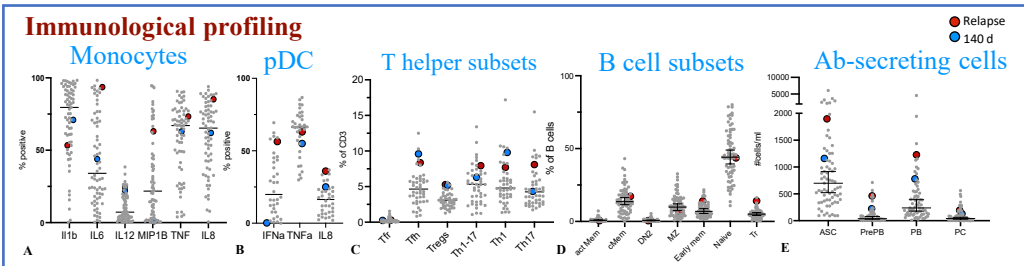

Fig 2. Immunological profiling at relapse and after 140 days. Percent of monocytes (A) or plasmacytoid dendritic cells (B) positive for the indicated cytokines after 3 hours of stimulation with a viral mimic (R848) Whole blood stimulated with the viral mimic R848 (TLR7/8) shows that, at relapse, the patient’s monocytes produce very high IL-6 and IL-8, with conspicuously low IL-1β. This indicates vigorous antiviral transcriptional responsiveness with a functional brake at the inflammasome step, consistent with a tolerized/overstimulated monocyte state; the subsequent normalization of IL-6/IL-8 suggests resolution of the acute drive. High production of antiviral IFN-a by plamacytoid dendritic cells (pDC). (C) Th subsets at relapse and after 140 days. The patient begins with conspicuously elevated pro-inflammatory T-cell subsets (especially Th17/Th1-17) and by 140 days shows a marked contraction of these populations, shifting toward a less inflammatory range. (D) B cell subsets, and (E) Antibody-secreting cells. At relapse the patient shows an early-memory skewed B-cell profile with elevated plasmablasts, a pattern consistent with a recent/ongoing antigen-driven response, plausibly antiviral. Red dots = the patient at relapse; blue dot = the same patient ~140 days later; grey dots = reference MS cohort (treatment-naïve or therapy-switch). Horizontal bars show cohort medians with 95% CI.

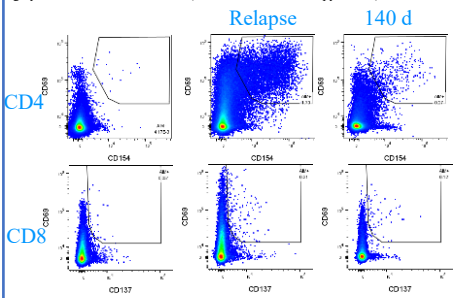

Fig.3. Detection of EBV-specific T cells with the AIM assay. Left panels, unstimulated cells. Centre panel and right, cells stimulated with EBV peptide pools .

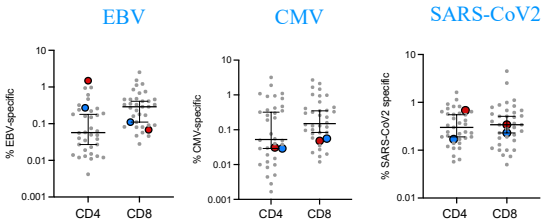

Fig.4. Virus specific T cell responses. Across the three viral pools tested, the AIM assay reveals a disproportionate EBV-specific response, strikingly high CD4+ AIM frequencies with scant CD8+ AIM reactivity, contrasting with the more modest, balanced responses to the other viruses, and aligning with our prior finding that insufficient EBV-specific CD8+ control associates with clinical relapses.

Conclusions. This multidimensional immunophenotyping reveals a **coordinated activation across adaptive and innate arms** of the immune system. The high frequency of EBV-specific CD4+ memory T cells coupled to the paucity of CD8 EBV-specific cells, to a surge in plasmablasts and hyper-reactive monocytes all converge on a scenario of subclinical or active relapse, characterized by antigen-driven immune reactivation. These findings reinforce the relevance of viral immunity and trained innate circuits in early MS and may provide immunological correlates of disease activity beyond clinical symptoms.

References: Bjornevik Ket al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022 Jan 21;375(6578):296-301; Aloisi F, Salvetti M. EBV infection drives MS pathology: Yes. Multiple Sclerosis Journal. 2024;30(4-5):483-485; Angelini DF et al., . Increased CD8+ T cell response to Epstein-Barr virus lytic antigens in the active phase of multiple sclerosis. PLoS Pathog. 2013;9(4). Amit Bar-Or, Rui Li, Cellular immunology of relapsing multiple sclerosis: interactions, checks, and balances. Lancet Neurol 2021; 20: 470–83.