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COMMENTARY

B cells and multiple sclerosis spinal cord pathology

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Once people with multiple sclerosis enter the progressive clinical phenotype of their disease, they often develop a syndrome resembling chronic myelopathy dominated by deteriorating spastic paraparesis, bladder, sexual and bowel dysfunction and lower limb sensory loss (10). Nevertheless, MS pathology in the spinal cord is significantly less well studied than in the brain, perhaps in part, due to the more laborious dissection involved (6). However, there has been renewed interest in the MS spinal cord, not least through efforts using magnetic resonance imaging to improve visualization and quantitation of subtle changes in the spinal cord thereby providing better short-term predictors of clinical change (4,14). In this edition of Brain Pathology, Reali and co-workers explore the role of meningeal B cells in the spinal cord (13). The authors selected three spinal cord samples from each of 22 progressive MS cases, half of which were found to have follicle-like clusters (FLC^+) in the meninges of the brain, whilst the other half did not (FLC^-). They then investigated the composition of the inflammatory infiltrate in the meninges and the perivascular and parenchymal grey and white matter of the spinal cord. Similar to earlier studies by the same group exploring the potential role of meningeal inflammation in the brain for cortical demyelination and neuronal loss (8,9), significant association was detected between the degree of inflammation and spinal cord pathology characterised by a greater degree of lymphocyte infiltration of the spinal leptomeninges, perivascular spaces and parenchyma, microglial activation, demyelination and axonal loss. Thus, spinal cord involvement could easily contribute to the deterioration in lower limb function noted in people with FLC in the brains (8). Of particular interest is their finding of a correlation between parenchymal spinal cord damage and the density of B cell, but not T cell, infiltrates in the cord meninges suggesting a prominent role of B cells in the pathogenesis of progressive MS. The observation that a topographic association between meningeal inflammation and parenchymal damage cannot only be detected in the forebrain (ie, in the subpial cortex), but also in the spinal cord (ie, in the subpial white matter and the underlying grey matter), supports a rather direct pathogenetic role of this meningeal infiltrate with TNF, IL6, IFNγ, CXCL13 and Semaphorin A (3) all suggested candidate mediators, more than 100 years after the close relationship between the subarachnoid space and MS lesions in the subpial parenchyma led Otto Marburg to hypothesize a toxic 'soluble 'factor'. Reali and coworkers' paper is timely: Despite the undisputed relevance of downstream mechanisms, such as oxidative stress, metabolic failure and excitotoxicity (5), the importance of B cells in progressive MS has been underpinned through successful phase III trials of immunotherapies with major impact on B cell subsets, including ocrelizumab (11) and siponimod (7). Against the backdrop of these clinical observations, and studies on the etiology of MS, Reali et al.'s quantitative immune phenotyping combined with standard neuropathology support the notion that B cells play a major role in MS pathogenesis (1). Another interesting feature of the work by Reali and colleagues is the significant microglia and macrophage activation in both FLC^+ and FLC^- cases, compared to controls (13). Whilst the lack of a difference between the two MS groups may be due to a limited sample size, one may speculate that a proportion of the tissue damage facilitated by the sequestered immune response in progressive MS is driven by microglial/ macrophage activity that is, at least in part, independent from a myelin antigen-specific, adaptive immune response (12). And whilst some success of treating progressive MS can be attributed to peripheral B cell depletion and modulation (1), clearing the central nervous system of FLC using CNS-penetrant and active immunotherapeutics will be the essential human experiment to demonstrate the causal importance of these B cells. The tools are perhaps on hand to achieve this goal (2). Reali et al.'s work provides yet more support that such studies are now worth undertaking.

CONFLICT OF INTEREST

KS has received consultancy and presentation fees from Biogen, Bayer HealthCare, EMD-Serono, Merck KG Aa, Novartis, Roche, Sanofi Genzyme and Teva. DB has received consultancy and presentation fees from Canbex Therapeutics, Japan Tobacco, Merck and Roche.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed.

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