Peripherally derived macrophages as major phagocytes in MOG encephalomyelitis

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An inflammatory demyelinating disease of the CNS with antibody against myelin oligodendrocyte glycoprotein (MOG-IgG) is now accepted as a discrete disease category of MOG encephalomyelitis (MOG-EM).1 Previous case studies described abundant accumulation of phagocytic cells (either Iba1+ and/or CD68+) at the active demyelinating lesions of MOG-EM.2–5 However, both Iba1 and CD68 can be expressed in either the microglia or macrophage.6 Recently, transmembrane protein 119 (TMEM119) has been proposed to be a reliable microglial marker that discriminates resident microglia from blood-derived macrophages in the inflamed human brain.6

Here, we discuss the immunohistochemical findings in a patient with MOG-EM using a specific marker for microglia, TMEM119.6

Case report

A 34-year-old male patient presented with sudden disorientation in September 2018. The neurologic examination showed disturbed consciousness with a Mini-Mental State Examination score of 17. Brain MRI showed multiple enhancing and T2 high signal intensity (HSI) lesions in both periventricular and deep white matter of the cerebrum, cerebellum, and upper medulla oblongata (figure, A). A CSF analysis demonstrated a cell count of 20 cells/μL (18 lymphocytes) and a slightly elevated protein level (50 mg/dL). The oligoclonal bands were positive, and IgG index was 0.61. Whole-body 18F-fluorodeoxyglucose PET revealed multifocal white matter lesions with mild hypermetabolism suggesting active inflammation rather than the malignancy. Initial EEG showed no epileptiform discharge. Serum fluorescent antinuclear antibody, antineutrophil cytoplasmic antibody, human T-cell lymphotropic virus antibody, cryoglobulin, anticardiolipin antibody, anti-β2-glycoprotein 1 antibody, and aquaporin-4 antibody were all negative. CSF cytology test showed no evidence of malignant cell. We suspected acute disseminated encephalomyelitis (ADEM) at first, and high-dose IV methylprednisolone (IVMP, 1 g for 5 days) following oral prednisolone (60 mg/d) were administered. As the follow-up brain MRI revealed improvement in T2 HSI lesion volume, we gradually tapered out prednisolone over 1 month.

Two weeks after discontinuation of prednisolone (2 months after first attack), he developed the patient returned with acute confusion and a bilateral tingling sensation below the T6 sensory dermatome level. Spinal cord imaging showed a diffuse contiguous T2 HSI lesion in T3 to T5. Brain MRI revealed increasing multiple T2 HSI and enhanced lesions on the right temporoparietal white matter, right occipital lobe, and both high frontoparietal lobes suggesting...
aggravated state of demyelinating disease or malignancy (figure, B). Because of diagnostic uncertainty, a stereotactic brain biopsy was performed in gadolinium-enhancing lesion of the right parietal lobe in early November 2018. He was treated again with IVMP. Serum MOG-IgG1 antibodies were detected by flow cytometry as described previously (figure, L and M).

The neuropathology revealed severe demyelination with diffuse infiltration of the foamy CD68+ phagocytic cells, focal mild perivascular lymphocytic infiltration, reactive astrogliosis, and a few Creutzfeldt cells. CD68+ cells were abundant in diffuse parenchymal lesion, but all of them were negative for TMEM119. Many of CD3+ or CD8+ T cells were observed in the brain parenchyma and perivascular area, whereas CD20+ B cells were observed only in the perivascular area (figure, C–K, and N). Brain tissue from a patient with glioblastoma was used as a positive control for TMEM119 staining, which revealed abundant TMEM119-positive cells.

Discussion

We report a case showing histopathologic characteristics of MOG-EM focusing on the origin of phagocytic cells. To identify the origin of these abundant phagocytic cells can be important in understanding the pathogenesis of MOG-IgG-associated disease. Our patient presented with an ADEM-like disease, and his neuropathologic findings revealed severe demyelination with infiltration of CD68+ TMEM119+ macrophages, T cells in the brain parenchyma, perivascular B cells, and absence of TMEM119+ microglia.
There are a few previous biopsy studies describing the histopathology in patients with MOG-EM, which showed inflammatory demyelination.\textsuperscript{2–5} Although others did not distinguish microglia from macrophage, Ikeda et al.\textsuperscript{5} proposed that the Iba-1\textsuperscript{+} cells in the brain lesion of a patient with MOG-EM were microglia based on cell morphology. Nevertheless, the morphology of microglia/macrophage can change according to external signals with pathogen and damage-associated signals. Recently, TMEM119 has been used as a marker that can distinguish brain resident microglia from blood-derived macrophages in the inflamed human brain tissue.\textsuperscript{6} Our data, using this marker, suggest that the CD68\textsuperscript{+} TMEM119\textsuperscript{+} cells in our MOG-EM patient’s brain tissue are active macrophages recruited from the peripheral circulations. This finding can be important in understanding the pathogenesis and in developing the treatment strategy of MOG-EM. However, the ratio of macrophage/microglia in the pathology of IDD can depend on the stage of the biopsied lesion,\textsuperscript{8} the expression of TMEM119 on microglia can also be downregulated on its activation,\textsuperscript{6} and further studies with larger samples including very early lesions are needed for the exact pathophysiology of MOG-EM.

In conclusion, we identified that macrophages rather than the microglia were the major phagocytic cells in the active demyelinating lesions of MOG-EM. Further studies on the detailed immune mechanism of these abundant macrophages infiltration/recruitment are needed.

Acknowledgment

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Appendix

Appendix (continued)

| Name                  | Location                          | Role          | Contribution                              |
|-----------------------|-----------------------------------|---------------|------------------------------------------|
| Patrick J. Waters     | John Radcliffe University Hospital, Oxford, UK | Author        | Data acquisition; analysis; critical reading of the manuscript; and read and approved the final manuscript |
| Moonhang Kim          | Seoul National University Hospital, Seoul, Republic of Korea | Author        | Data acquisition and analysis; critical reading of the manuscript; and read and approved the final manuscript |
| Youn Soo Choi         | Seoul National University College of Medicine, Seoul, Republic of Korea | Author        | Data acquisition and analysis; critical reading of the manuscript; and read and approved the final manuscript |
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| Jung Joon Sung        | Seoul National University Hospital, Seoul, Republic of Korea | Author        | Critical reading of the manuscript and read and approved the final manuscript |
| Sung Hye Park         | Seoul National University Hospital, Seoul, Republic of Korea | Co-corresponding author | Study conception and design; data acquisition and analysis; statistical analysis; critical reading of the manuscript; and read and approved the final manuscript |
| Sung Min Kim          | Seoul National University Hospital, Seoul, Republic of Korea | Guarantor and corresponding author | Study conception and design; drafting of the manuscript; data acquisition and analysis; critical reading of the manuscript; and read and approved the final manuscript |

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