

## Commentary: Is ADEM a subgroup of MS?

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### Article Info

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### ABSTRACT

Acute disseminated encephalomyelitis (ADEM) and Multiple sclerosis (MS) are both immunologically mediated inflammatory demyelinating disease of the CNS. ADEM and MS have long been considered as a separate disease entities, but clinical differentiation of ADEM from the first attack of MS is often difficult because of overlapping clinical features. Pathologically, perivenous demyelination and discrete confluent demyelination (plaque) have been generally regarded as the hallmark of ADEM and MS, respectively. It is also known that in contrast to MS, which shows quite diverse heterogeneous pathologic patterns, ADEM shows generally homogenous pathological features of inflammatory demyelination. However, hybrid cases showing pathological features of both ADEM and MS do exist, suggesting that ADEM may share some common underlying pathologic mechanisms with certain stages or subgroups of MS.

### Text

Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) have been considered as clinically and pathologically distinct phenotype of inflammatory demyelinating disease of CNS<sup>1,2</sup>. ADEM, typically but not always anteceded by infectious illness or vaccination, presents with a monophasic course with relatively favorable prognosis, while MS typically exhibits a relapsing and remitting course with accumulating neurological deficits with each exacerbation. However, despite several clinical and/or radiological criteria proposed to differentiate ADEM from MS, none has been proven to unequivocally separate them. With many similarities in clinical presentation, MRI findings and putative pathogenesis, Hartung and Grossmann speculated that ADEM may not be a distinctive disease but a part of the MS spectrum<sup>3</sup>. On the other hand, pathological differentiation between ADEM and MS has been regarded as most reliable. ADEM is characterized by perivenous demyelination and MS by confluent demyelination, with these two patterns seldom coexisting in a single patient<sup>4</sup>.

We have recently experienced a patient clinically diagnosed as ADEM whose brain biopsy revealed pathologically features indistinguishable from active lesions of MS in addition to the characteristic foci of perivenular inflammation and demyelination of ADEM<sup>5</sup>. This mini-review is based on this report.

### Case presentation

Detailed clinical information of the patient has been reported previously<sup>5</sup>. Briefly, a 51-year female presented with progressive aphasia and right-sided hemiparesis after a month history of new onset increasing headache. There was no apparent antecedent flu-

like illness or history of vaccination. Cerebrospinal fluid (CSF) examination revealed slight pleocytosis and increase in protein and myelin basic protein (MBP). There were no oligoclonal bands. Brain MRI revealed multifocal subcortical lesions mainly involving subcortical white matter of the left temporal and parietal lobes without enhancement.

Because of the rapid progression of her symptoms with the new onset of focal seizures, a brain biopsy was performed. She was then started on intravenous methyl prednisolone followed by oral prednisolone taper. The patient responded remarkably both clinically and radiologically, and was discharged two month later. She was able to resume her former daily social activities. At the time of this writing, 9 years later, there has been no clinical recurrence.

The brain biopsy revealed both patterns of perivenular/perivascular demyelination and a confluent demyelination in the cerebral cortices and in subcortical white matter. They were associated with perivascular cuffing of B and T lymphocytes. The leptomeninges also revealed an inflammatory cell infiltrates, composed of B and T cells, occasionally infiltrating into the Virchow-Robin spaces. Immunohistochemistry with MBP or CNPase using thicker sections, revealed areas of subpial demyelination<sup>5</sup>.

The representative perivenous demyelination of this case is shown in the Figure (A-H). They were immunostained on serial sections for various cell markers (CD4; helper T cell marker, CD8; cytotoxic T cell marker, CD20; a B cell marker, HLA-DR; microglial marker). The perivascular inflammatory infiltrates were immunoreactive for HLA-DR, CD20, CD4 and CD8 (E-H). In the area of perivenous demyelination, there was a sheet-like proliferation of HLA-DR positive microglial cells. Activated microglia as manifested by rich cytoplasm and ramified cell processes could also be seen around the demyelinating lesion (E). There was a clear tendency of CD20 positive B cells to be localized in the perivascular space limited by glia limitans (B, F). On the other hand, CD4 and CD8 positive T cells were found scattered in the perivenular demyelination and also found infiltrating in the surrounding brain parenchyma (G, H).

### On the coexistence of ADEM and MS pathology

It remains unsettled if ADEM is immunopathologically distinct from MS or may share common underlying pathologic mechanisms with MS. Similar controversy also exists concerning distinction of the multiphasic form of ADEM (MDEM) from relapsing MS<sup>6</sup>. This seems partly because, in contrast to those of MS, few cases of ADEM with immunohistochemical analysis have been available so far, including MEDM variant. A variability in the appearance and nature of T and B lymphocytes has been reported<sup>7</sup>. In one fulminant case of ADEM, stereotaxic biopsy of the

frontal white matter showed perivenous inflammation and demyelination with presence of CD3 positive, CD8 positive, but not CD20 positive B cells<sup>8</sup>.

In contrast to ADEM, which shows generally homogenous pathological features with known similarities to experimental autoimmune encephalitis, MS is known to be pathologically diverse. According to Lucchinatti, four patterns could be discerned in MS: Pattern I lesions show inflammatory lesions made up of T cells and macrophages alone: Pattern II lesions contain immunoglobulin and complement: Pattern III is a distal dying back oligodendroglialopathy: and Pattern IV is characterized by primary oligodendroglial degeneration<sup>9</sup>.

In the case we have reported, both the perivenous demyelination and the confluent demyelination, pathognomonic feature for ADEM and MS respectively, were recognized<sup>5</sup>. The demyelinating pattern of the case we have reported seems most consistent with Pattern I, in that microglia/macrophage and T cells infiltration was evident in the active demyelinating lesions in the absence of IgG deposition by immunohistochemistry, and that there was no apparent features suggestive of oligodendrocyte degeneration. In addition, meningeal inflammation associated with subpial cortical demyelination was also recognized, which have been reported in early and progressive stage of MS<sup>10-13</sup>. However, the occurrence of leptomeningeal inflammation and subpial demyelination have also been described in ADEM<sup>4,14</sup>.

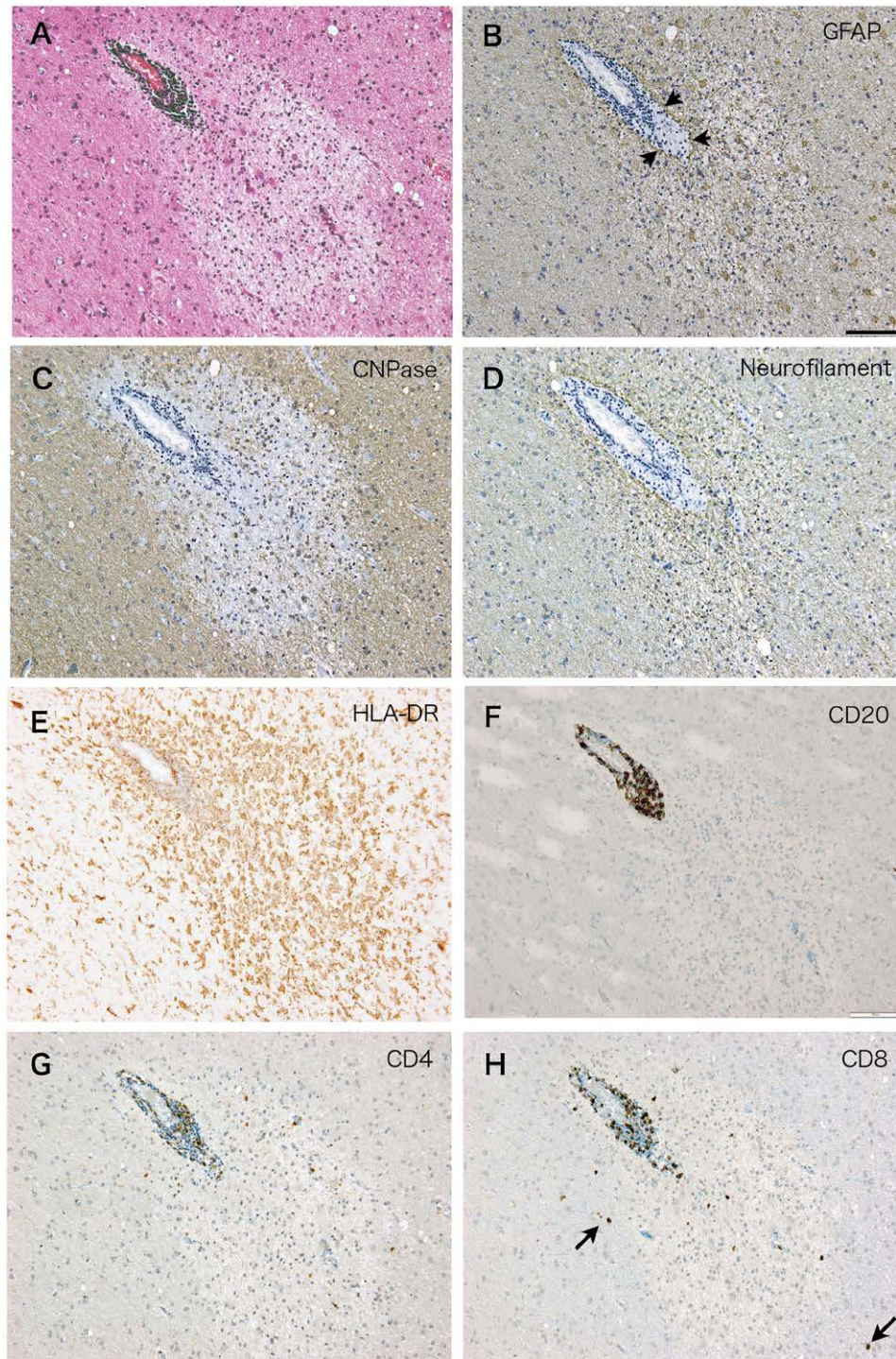
### Is ADEM a subgroup of MS?

There have been several recent case reports illustrating difficulties in the clinical differentiation between ADEM and MS, in which pathological studies seem to have played a key role.

Hoche et al. reported a 16 year-old patient clinically diagnosed as ADEM whose brain biopsy showed histological features of active MS (pattern I according to Lucchinetti) without perivenous demyelination<sup>15</sup>.

Popescu et al. reported on a 33 year old patient who started to complain of headache one week after an upper respiratory tract infection. She was found to have a solitary lesion in the occipital cortex and a biopsy demonstrated cortical demyelination associated perivascular infiltrates consisting of T and B cells. The diagnosis of MS was subsequently confirmed through clinical follow up with the new appearance of white matter lesions on MRI<sup>10</sup>.

Guenther et al. reported an autopsy case of a 19 year-old clinically diagnosed as ADEM who suddenly died of sepsis. Autopsy revealed multiple foci in a confluent demyelination pattern in the absence of areas of perivenular demyelination. The author interpreted that the case could represent either a first demyelinating event in a case of MS



**Figure [A-H]:** Serial sections of the perivenular demyelination characteristic for ADEM in the case<sup>4</sup> stained with H.E.(A), and immunostained with antibody to GFAP (B), CNPase (C), neurofilament (D), HLA-DR (E), CD20 (F), CD4 (G), CD8 (H), respectively. In the area of perivenular demyelination, there was an increase in the number of HLA-DR positive microglia (E) and reactive astrocytes (B). Arrowheads in (B) indicate gliia limitans defining perivascular infiltrates. CD20+ B cells (F) tend to be restricted in the perivascular space, while CD4+ T cells (G) and CD8+ T cells (H) are more scattered in the area of perivascular demyelination. Arrows in (H) indicate CD8 positive cells apparently outside of the demyelinating lesion. Bar= 50µm.

with ADEM-like clinical presentation or a case of ADEM with an unusual MS-like pattern of demyelination<sup>16</sup>.

Yidiz et al. reported a 35 year-old woman with 14-year history of relapsing-remitting MS who developed

a hyperacute form of ADEM (Acute Hemorrhagic Leukoencephalitis AHLE), a diagnosis confirmed by brain biopsy. Interestingly, this patient had started experiencing typical MS relapses after the ALHE episode had resolved.

The authors believe that MS and ADEM occurred independently in this patient<sup>17</sup>.

In comparative study of clinical features between those with and without perivenous demyelination using biopsy/autopsy material, Young et al. showed that perivenous demyelination is associated with a meningoencephalitic presentation and a monophasic course. Three patients of perivenous demyelination cohort showed both perivenous and confluent patterns and two of them had relapsed. One patient out of ten with perivenous pattern relapsed. On the other hand, 15 out of 91 patients of the confluent cohort showed monophasic course (mean 7.1 years of follow-up), and was diagnosed as isolated demyelinating syndrome<sup>4</sup>.

Together with these cases illustrating the clinical overlap of MS and ADEM, and the presence of hybrid cases with overlapping pathological features as we have reported, we believe that the possibility of chance association of MS and ADEM seems very unlikely, if not completely excluded. It seems more likely that the CNS pathology of ADEM may share common immunopathologic features of active MS, in which participation of immune effector cells consisting of T and B cells, and activated microglia are essential features<sup>18-21</sup>. Conceivably, perivenous demyelination and confluent demyelination may have same pathologic basis and differ only in the stage and the appearance of the lesions. Under certain conditions, small perivenous demyelination may evolve and coalesce into a confluent demyelination.

## Conclusion

ADEM and MS have been considered as distinct phenotypes, pathologically characterized by perivenous demyelination vs. confluent demyelination. However, cases of the first clinical episode of CNS demyelination showing both pathological features of ADEM and MS do exist, suggesting that CNS pathology of ADEM may share common pathologic mechanism(s) with certain subgroups of MS.

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