Justine J. Wang, MBBS,
FRACP

Zane Jaunmuktane, MD,
FRCPath

Catherine Mummery,
PhD, FRCP

Sebastian Brandner, MD,
FRCPath

Siobhan Leary, MD,
FRCP

S. Anand Trip, PhD,
FRCP

INFLAMMATORY DEMYELINATION WITHOUT ASTROCYTE LOSS IN MOG ANTIBODY-POSITIVE NMOSD

We report a patient with neuromyelitis optica spectrum disorder (NMOSD) with antibodies against myelin oligodendrocyte protein (MOG) and seronegative for aquaporin-4 (AQP4) presenting with relapsing-remitting longitudinally extensive transverse myelitis (LETM) and cerebral tumefactive demyelinating lesions. Neuropathology showed active inflammatory demyelination with relative preservation of astrocytes.

Case report. A 67-year-old woman with a history of hypothyroidism presented with 2 distinct symptomatic episodes of LETM. At initial presentation she had a T10 dissociated sensory level, sensory ataxia, and sphincter dysfunction, from which she recovered spontaneously. One month later, she presented with burning upper limb and thoracic pain, right lower limb weakness, and sphincter dysfunction. Initial spinal MRI showed a continuous T2-hyperintense central cord lesion from T2 to T9 with mild cord expansion and patchy enhancement; MRI 1 month later showed a new central cord T2 hyperintensity from C5 to T3 (figure, A and B). CSF examination was bland, with matched CSF/serum oligoclonal bands. AQP4 antibodies were negative. She made an almost complete recovery after 3 days of IV methylprednisolone, then oral prednisone 50 mg daily tapered over 5 weeks.

Five months later, the patient presented to our institution with dysarthria and left facial weakness, rapidly progressing within 24 hours to left hemiparesis, lower limb flaccid paraparesis with extensor plantar responses, and a dissociated T10 sensory level. Brain MRI revealed 3 ill-defined white matter lesions in the right cerebral hemisphere (frontal corona radiata, posterior parietal lobe, and temporal pole), sparing the cortex, associated with extensive vasogenic edema, patchy enhancement, and peripheral concentric diffusion restriction. A few small lesions in the left hemispheric white matter and the right pons were also noted. Spinal MRI showed new T2 hyperintensity from T12 to the conus (figure, C–E). Visual evoked potentials were normal. Extensive blood investigations were normal or negative, including HIV and syphilis serology, serum angiotensin converting

enzyme level, and vasculitic markers. Repeat testing for AQP4 antibodies was negative.

Due to concerns of a neoplastic process, biopsy of the right frontal lesion was undertaken.

Histology showed a sharply demarcated lesion, with macrophage-rich active inflammatory demyelination, with prominent loss of myelin, but relative preservation of axons (figure, Q–S). Immunostaining with glial fibrillary acid protein (GFAP) confirmed reactive astrocytes within and surrounding the lesion (figure J, O, and T). In the demyelinated white matter, there were dense perivascular cuffs of small T lymphocytes and fewer B lymphocytes. Immunostaining for SV40 (surrogate marker for JC virus infection) was negative.

A cell-based assay using C-terminal-truncated human MOG later identified antibodies against full/short-length MOG, including the more specific immunoglobulin G1 (IgG1) assay.¹ After treatment with IV methylprednisolone, plasmapheresis, and tapering oral prednisolone, the patient was started on immunosuppression with azathioprine. There was an incomplete recovery with residual moderate lower limb pyramidal pattern weakness, requiring a frame to mobilize and a urinary catheter, and neuropathic pain remained.

Discussion. Autoantibodies against MOG have been identified in patients with acute disseminated encephalomyelitis and pediatric clinically isolated syndrome, and recently identified in patients with AQP4-seronegative NMO/NMOSD.^{1,2} Our patient had anti-MOG IgG1 antibody and repeatedly tested negative for AQP4 antibody. She fulfilled the diagnostic criteria for NMOSD with 3 distinct episodes of LETM³ and tumefactive cerebral lesions.

Abnormal MRI brain findings have been seen in 37.5%–66% of MOG-seropositive patients with NMOSD. They were nonspecific white matter, periventricular, deep gray matter, or pontine lesions.^{1,2} There have only been 2 cases reported of large hemispheric or tumefactive lesions.^{1,4} Our patient had a less common presentation with symptomatic large hemispheric tumefactive lesions, concurrent with the third episode of LETM, which is a core clinical characteristic for NMOSD.³

Histopathology of active lesions from AQP4-seropositive patients with NMO showed inflammatory infiltrate with reduction or loss of GFAP-positive

MRIs: (A) T2-weighted MRI of the thoracic spine during the first attack, with a longitudinally extensive T2-hyperintense central cord lesion from T2 to T9, with mild cord expansion. (B) T2-weighted MRI of the cervical and upper thoracic spine during the second attack shows new longitudinally extensive central cord T2 hyperintensity from C5 to T3. (C) T2-weighted MRI of the cervico-thoracic spine during the third attack shows longitudinally extensive T2-hyperintense lesion C5-T3, with less T2-hyperintense signal extending continuously down to T9. (D, E) T2 fluid-attenuated inversion recovery images of MRI brain during the third attack show ill-defined large tumefactive lesions with extensive vasogenic edema in the right frontal corona radiata, posterior parietal lobe, and temporal pole. Biopsy of the right frontal lesion was undertaken (red box). Histopathology (F-T): Overview of the brain biopsy (F-J) shows pathological tissue (blue square in F, corresponding to P-T) admixed with fragments of intact brain parenchyma (yellow square in F, corresponding to K-O). The perilesional tissue (K-O) shows overall preserved cytoarchitecture (K, L) with occasional axonal spheroids (M, arrow), mild microglial activation (N), and prominent reactive astrogliosis (O). The lesional tissue (P-T) shows marked tissue disruption (P). Immunostaining for myelin (Q) highlights prominent myelin loss, and staining for neurofilaments (R) shows relative preservation of axons. There are frequent macrophages (S) and reactive astrocytes in the demyelinating areas (T). Scale bar: 1 mm in F-J, 50 μ m in K-O, 100 μ m in P-T.

astrocytes, or astrocyte cytologic abnormalities.⁵ In contrast, our patient's brain lesion demonstrated active inflammatory demyelination, with relative preservation

of GFAP-positive astrocytes within and surrounding the lesion. This is consistent with a report of a MOG-seropositive patient with NMO with CSF

biomarkers during an acute attack showing markedly elevated levels of myelin basic protein, but undetectable GFAP.⁶

Our patient's neuropathologic findings were similar to those described in tumefactive demyelinating lesions associated with multiple sclerosis. This is the first neuropathologic report of MOG-seropositive NMOSD. A report of MOG-seropositive relapsing-remitting encephalomyelitis with brainstem and tumefactive bihemispheric lesions, but no LETM, showed similar brain histopathology with active inflammatory demyelination, reactive astrocytes, and terminal complement activation.⁷

Our case provides further evidence of severe demyelination without astrocyte loss in MOG-seropositive NMOSD, distinguishing it from AQP4-seropositive NMO. It also expands the clinical phenotype for MOG antibody-associated demyelinating disorders.

From the National Hospital for Neurology & Neurosurgery, UCLH NHS Foundation Trust and UCL Institute of Neurology, London, UK.

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Correspondence to Dr. Trip: anand.trip@uclh.nhs.uk

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