



Case report

MOG antibody disease manifesting as progressive cognitive deterioration and behavioral changes with primary central nervous system vasculitis

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ABSTRACT

We report a 60-year-old male with anti-myelin oligodendrocyte glycoprotein (MOG) antibody who developed progressive cognitive deterioration and behavioral changes, with no other focal signs, over 9 months. MRI showed numerous T2-hyperintense lesions with partial contrast enhancement in white and grey matter of cerebrum, cerebellum and spinal cord. A brain biopsy revealed perivascular inflammatory cell infiltration, disturbed vascular continuity and no demyelination, indicative of a lymphocytic pattern of primary CNS vasculitis (PCNSV). Contrast enhancement disappeared after immunotherapy; however, cognitive impairment was not improved. Neurologists should note that MOG antibody disease can present as immunotherapy-resistant progressive cognitive impairment with PCNSV-like histopathology.

1. Introduction

Anti-myelin oligodendrocyte glycoprotein (MOG) antibody has been identified in serum and/or cerebrospinal fluid (CSF) in various neuroimmunological disorders, such as optic neuritis, transverse myelitis, acute disseminated encephalomyelitis (ADEM) and cortical encephalitis (Jurynczyk et al., 2017; Nakashima, 2015). However, there is little literature describing histopathological features, especially for adult cases. Here, we describe an adult patient with anti-MOG antibody who presented with slowly progressive cognitive impairment and behavioral changes that were resistant to immunotherapy. Intriguingly, a brain biopsy revealed histopathological features of primary CNS vasculitis (PCNSV) with no apparent demyelination.

2. Case report

A 60-year-old male was referred and admitted to our hospital because of slowly progressive cognitive decline and personality changes, with disseminated brain lesions on MRI. He initially developed moderate headache that lasted for 2 weeks, followed by mild memory

problems 9 months before admission. Subsequently, he had progressive general fatigue, memory impairment and low mood. The patient had been diagnosed with depression and treated at a psychiatry outpatient clinic. On admission, neurological examination revealed a confused, irritable state with disorientation (Glasgow Coma Scale, E4V4M6), decreased vigilance, short-term memory impairment and mild bilateral hyperreflexia, but there were no signs of cranial nerve, motor, sensory or autonomic system involvement. His Mini-Mental State Examination score was 11 out of 30.

Complete blood counts and serum chemistry were generally normal with no evidence of infection, metabolic disorders or autoimmune diseases. Anti-neutrophil cytoplasmic antibody, anti-N-methyl-D-aspartate receptor antibody, anti-voltage-gated potassium channel antibody and anti-glutamic acid decarboxylase antibody were all negative. The CSF was mildly hypercellular (12/μL, all mononuclear cells), with elevated levels of total protein (58 mg/dL), IgG index (1.30), myelin basic protein (MBP, 121 pg/mL) and interleukin-6 (32.5 pg/mL). Oligoclonal IgG bands were negative. MRI T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images disclosed disseminated hyperintense lesions in the deep and subcortical white

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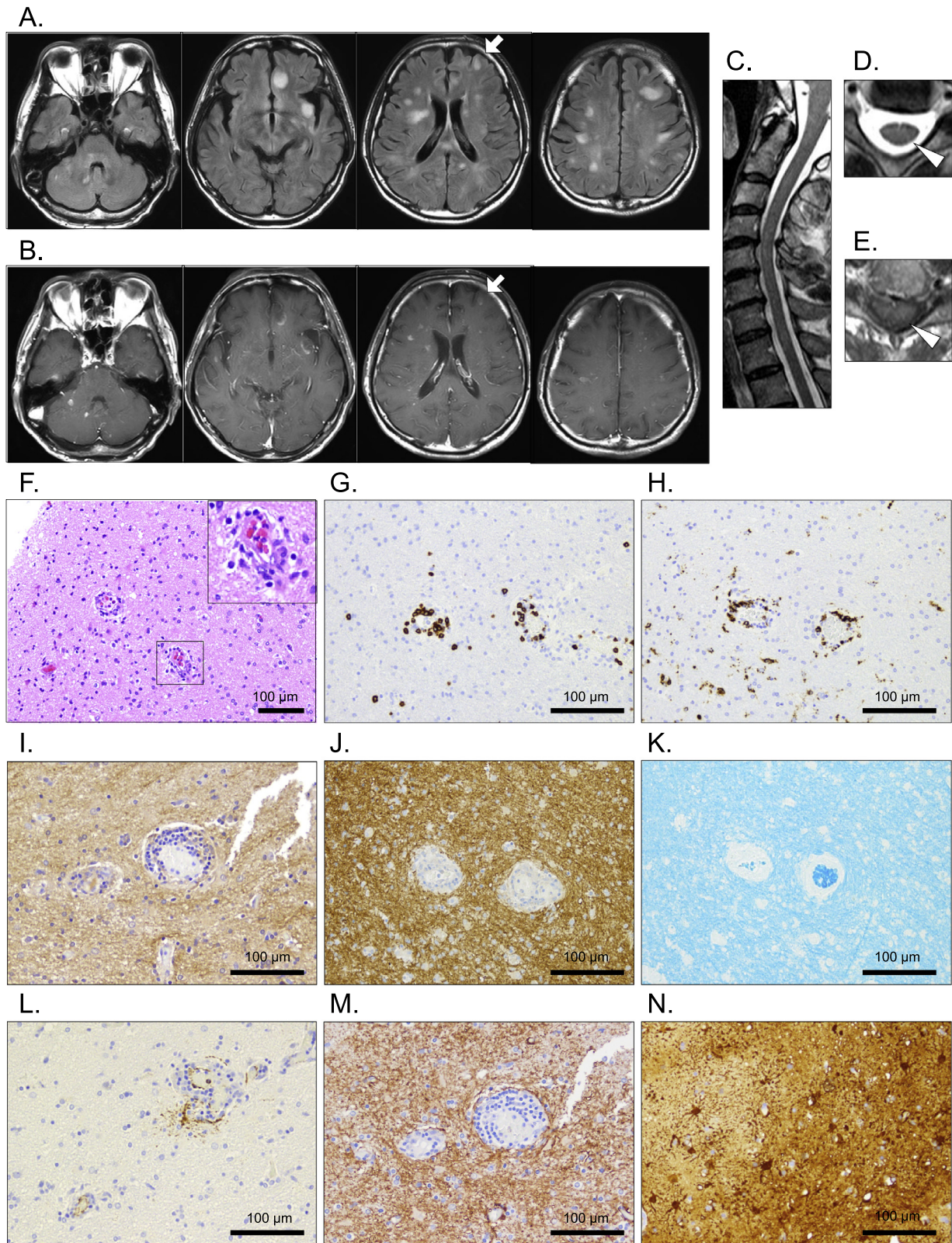


Fig. 1. MRI images on admission and brain histopathology. (A) Axial fluid-attenuated inversion recovery (FLAIR) images of brain; (B) axial gadolinium-enhanced T1-weighted images of brain (arrows, the biopsied lesion); (C) sagittal; (D) axial T2-weighted; and (E) axial gadolinium-enhanced T1-weighted images of cervical spinal cord (arrowheads, the lesion at the level of C4). (F) Perivascular infiltration of mononuclear cells (hematoxylin-eosin staining); (G) perivascular infiltration of T lymphocytes (immunostaining for CD3); (H) perivascular infiltration of macrophages (immunostaining for CD68); (I-K) preserved myelin sheath (I: immunostaining for myelin oligodendrocyte glycoprotein, J: immunostaining for myelin basic protein, K: Luxol fast blue staining); (L) impaired vascular continuity (immunostaining for α -smooth muscle actin); (M) preserved aquaporin-4 (immunostaining for aquaporin-4); (N) reactive astrocytes (immunostaining for glial fibrillary acid protein).

matter and adjacent cerebral cortex, corpus callosum, basal ganglia, hypothalamus, cerebellum, brainstem and cervical spinal cord (Fig. 1A,C,D). Some lesions showed partial or open-ring contrast enhancement (Fig. 1B,E). There was no evidence of malignancy in a random skin biopsy and no increased uptake in an ^{18}F -fluorodeoxyglucose positron emission tomography-CT scan. Electroencephalography showed moderately impaired dominant rhythm with no epileptic discharges.

A brain biopsy was performed from a frontal lobe lesion with contrast enhancement to rule out the possibility of primary central nervous system lymphoma. Histopathological examination revealed inflammatory cell infiltration of T lymphocytes and macrophages in the small blood vessels and perivascular brain tissue (Fig. 1F–H). There were no malignant cells, including lymphoma. No apparent demyelination was detected by immunohistochemistry with anti-MOG and anti-MBP antibodies or with Luxol fast blue staining (Fig. 1I–K). Notably, immunoreactivity of α -smooth muscle actin was disrupted in several inflamed blood vessels, indicating damaged vascular continuity (Fig. 1L). Reactive astrocytes, in which aquaporin-4 (Fig. 1M) and glial fibrillary acid protein (Fig. 1N) were well expressed, were abundantly present in the brain parenchyma. Thus, we considered the histopathological features compatible with PCNSV. We treated the patient with three courses of intravenous methylprednisolone therapy (1000 mg daily for 3 days) followed by oral prednisolone (50 mg/day with gradual taper). After treatment initiation, serum anti-MOG antibody at admission was found to be positive on a cell-based assay (titer 256 \times). Follow-up CSF tests were normal and MRI images showed mild brain atrophy, partial shrinkage of hyperintense lesions on FLAIR images and disappearance of contrast enhancement. Nevertheless, the patient's cognitive deterioration and behavioral changes were not improved; he was transferred to a psychiatric hospital because of his uncontrollable violent behavior and his family's wishes.

3. Discussion

We report an adult case of MOG antibody disease presenting as slowly progressive cognitive impairment and behavioral changes. We diagnosed the patient with PCNSV on the basis of histopathological findings, which were compatible with the lymphocytic pattern of PCNSV (Salvarani et al., 2015). However, serum anti-MOG antibody was later found to be positive. We consider that the present case is an atypical and intractable phenotype of MOG antibody disease.

MOG antibody disease has been recognized as a spectrum of autoimmune CNS disorders (Jurynczyk et al., 2017; Nakashima, 2015). Histopathological features of anti-MOG antibody-positive adult cases have been rarely reported. A 66-year-old patient with relapsing encephalomyelitis showed severe demyelination, inflammatory cell infiltration and complement activation (Spadaro et al., 2015), i.e. pattern II lesions of multiple sclerosis (Lucchinetti et al., 2000). Two adult patients who fulfilled the diagnostic criteria of ADEM were also reported to have histopathological findings of active, confluent demyelination, T cell-dominant inflammation and complement deposition, which were compatible with pattern II and III lesions of multiple sclerosis (Kortvelyessy et al., 2017; Lucchinetti et al., 2000). MRI features in the present case were similar to these cases; however, the histopathological features were clearly distinct from these reports and from typical cases of ADEM, especially the absence of demyelination. Although MBP in the CSF was minimally elevated, myelin sheaths were mostly preserved, as assessed with anti-MOG and anti-MBP immunostaining and Luxol fast blue staining. Interestingly, recent studies described anti-MOG antibody-positive encephalitis with normal levels of MBP in the CSF and no apparent demyelination histopathologically (Fujimori et al., 2017; Ogawa et al., 2017); however, no previous reports have shown PCNSV-like histopathology in anti-MOG antibody-

positive cases. It is also possible that other factors such as currently unknown autoantibodies were involved in the pathogenesis and that anti-MOG antibody was secondarily generated during the disease course.

Unfortunately, the memory disturbance and behavioral changes in our patient were not improved by immunotherapy, despite normalized CSF findings and resolution of contrast enhancement on MRI. We speculate that the delay in the diagnosis and the irreversible non-demyelinating brain damage affected the outcome in the present case. Immunotherapy may have been more effective if initiated at an earlier stage, without the 9-month delay resulting from a misdiagnosis of depression. Furthermore, a recent paper on pediatric patients showed that ongoing cognitive problems were observed in 10 out of 31 anti-MOG antibody-positive pediatric patients, even though all showed significant improvement of MRI abnormalities at follow-up (Hacohen et al., 2018). This report demonstrated that persistent cognitive problems may occur in MOG antibody disease, although the exact mechanism remains elusive. We believe that our case further expands the clinical spectrum of MOG antibody disease and that neurologists should be aware that MOG antibody disease can present as slowly progressive cognitive impairment with PCNSV-like histopathology.

Conflict of interest

None declared.

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