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LEADING TOPIC

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Tumefactive demyelinating lesion in patient with neuromyelitis optica spectrum disorder

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To the Editors

Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune, inflammatory and demyelinating diseases of the central nervous system (CNS) that predominantly affect the optic nerve and spinal cord. The most specific radiological feature in the acute phase of NMOSD is longitudinally extensive transverse myelitis (LETM) lesions extending over three or more vertebral segments with central cord predominance. The typical cerebral lesions involve the dorsal medulla, periependymal tissues surrounding the ventricular system, hypothalamus, thalamus, hemispheric white matter, and corticospinal tractus [1]. Extensive brain lesions are rare in NMOSD, and may indicate a poor prognosis. Extensive brain lesions tend to be more frequent in patients with high titres of AQP4-IgG who show loss of AQP-4 expression in neuropathological examination [2].

We present a case of seronegative NMOSD with LETM who developed a tumefactive demyelinating lesion six months after the initiation of rituximab therapy.

A 29-year-old Caucasian male presented with subacute onset, slowly progressive right hemiparesis. He described sensory disturbance in the right arm for 25 days and a right-sided hemiparesis for one week. His initial cranial magnetic resonance imaging (MRI) was normal, but cervical MRI revealed a contrast enhancing lesion located at the C1–2 level, which appeared as hyperintense on T2-weighted, and hypointense on T1-weighted images (Fig. 1A). The patient was referred to our neuroimmunology clinic since his weakness had increased and his cervical lesion progressed despite high-dose steroid treatment (Fig. 1B–1D). He had no previous disease or family history of autoimmune-neuroinflammatory disease. His neurological examination revealed right hemiparesis, mild weakness in the left upper extremity, and total right-sided sensory loss below C2 level. Screening for vasculitic and autoimmune diseases were normal. In the cerebrospinal fluid (CSF), protein level was 69.54 mg/dL (reference range: 15–45), cytology and culture were negative, IgG index value was 0.52, and oligoclonal bands were absent. Serum samples taken 10 days after high-dose steroid treatment were negative for AQP4 and myelin oligodendrocyte glycoprotein IgG antibodies. Although 10 more days of high-dose steroid therapy resulted in significant improvement, quadriparesis and urinary retention developed on the fifth day. A cervical MRI revealed a centrally located longitudinally extensive lesion with intense and heterogeneous contrast enhancement between the bulbus and C6 (Fig. 1E).

Plasma exchange for six sessions led to significant improvement once again. Intravenous infusions of 1,000 mg rituximab were administered twice, two weeks apart. Following a stable period of five months, he had an epileptic seizure. His neurological examination was normal, but cranial MRI revealed a tumefactive lesion with open-ring enhancement in the right frontal lobe (Fig. 1F, 1G). The previous cervical lesion had

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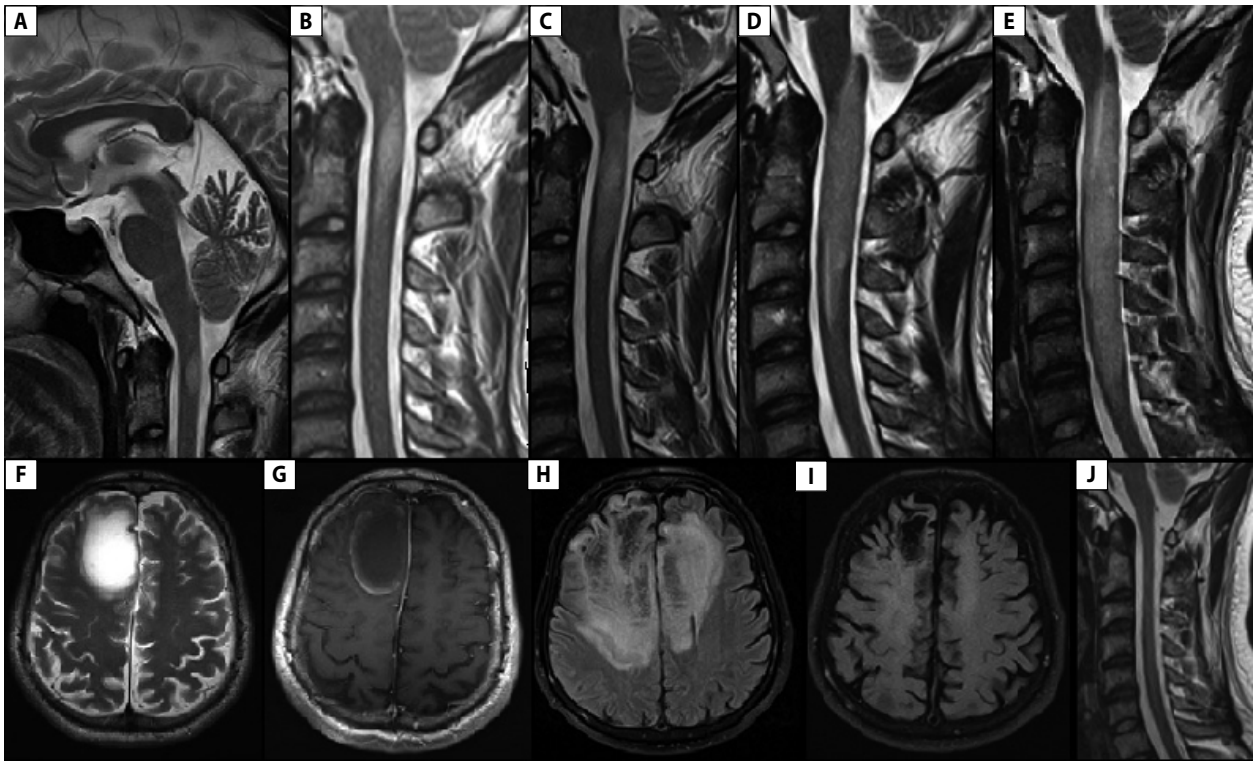

Figure 1. **A.** T2-weighted sagittal image demonstrating acute phase of transverse myelitis located at C1–2 level; **B–D.** Lesion progression after five days of high-dose methylprednisolone treatment; **E.** Lesion progression in longitudinal extensive transverse myelitis between bulbus and C6 level after 10 more days of high-dose methylprednisolone treatment; **F.** Axial T2-weighted image demonstrating tumefactive demyelinating lesion in right frontal lobe with surrounding vasogenic oedema following rituximab therapy; **G.** Axial T1-weighted image with open-ring enhancement; **H.** Axial fluid-attenuated inversion recovery (FLAIR) image demonstrating bifrontal lesion with mass effect; **I–J.** Follow-up MRI at six months showing significant improvement in cerebral and cervical lesions

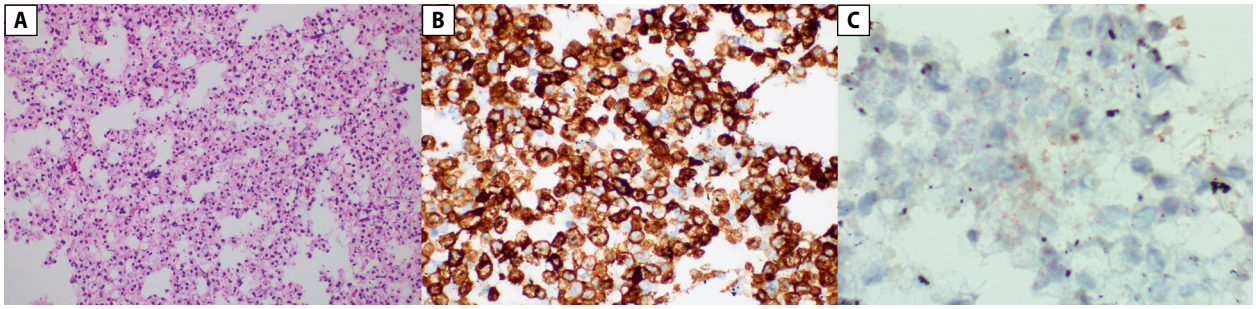

Figure 2. Histopathological and immunohistochemical analysis of brain biopsy; **A.** Aggregates of macrophages with clear, foamy cytoplasm and round nuclei (haematoxylin and eosin staining x 200); **B.** Macrophages strongly positive for CD163 (x 400). **C.** Myelin degradation demonstrated in macrophages' cytoplasm (MBP x 100)

regressed. Serum AQP4-IgG test performed at the fifth month after rituximab treatment was negative again. The CSF profile revealed elevated protein (960 mg/dL) and low glucose levels (27 mg/dL). There was a mild pleocytosis with 11 cells/μL, eight mononuclear, and three polymorphonuclear. A stereotactic brain biopsy was performed. Histopathological analysis revealed macrophage aggregates with clear, foamy cytoplasm and round nuclei (Fig. 2A). In the immunohistochemical study, macrophages were strongly positive for vimentin and CD163, a marker associated with M2 phenotype which has been shown to downregulate immune responses and has regenerative effects, and is also found on perivascular macrophages in demyelinating MS lesions [3] (Fig. 2B). The macrophages were weakly positive for CD68, CD45, CD33, and lysozyme and negative for glial fibrillary acidic protein (GFAP), olig2, OSCAR cytokeratine, epithelial membrane antigen (EMA),

and paired-box gene 8 (PAX8). Ki-67 proliferative activity was below 1%. Myelin degradation was demonstrated by myelin basic protein (MBP) immunohistochemistry in the macrophages' cytoplasm (Fig. 2C). Levetiracetam 1,000 mg/day was added to his therapy, and a high-dose steroid was given for 10 days.

One month later, he developed fever, impaired consciousness, quadriparesis and leftward conjugate gaze palsy. Cranial MRI showed a bifrontal lesion with a mass effect (Fig. 1H). His consciousness and gaze paresis improved after seven sessions of plasma exchange and 1,000 mg of rituximab infusion. As maintenance therapy, a single dose of 0.4 g/kg intravenous immunoglobulin was administered once a week for the first month, then once every 15 days for two months, and then once a month for four months. Follow-up MRI at six months showed significant improvement in both frontal and cervical lesions (Fig. 1I, 1J) and mild left-sided hemiparesis remained as sequelae. No other relapse has occurred so far. The patient was diagnosed with seronegative NMOSD according to the 2015 revised consensus criteria. The lack of antibodies in serum samples could be a result of previously initiated immunosuppressive treatment.

A tumefactive demyelinating lesion (TDL) is an acute, tumour-like lesion which may cause mass effect. TDLs showing open-ring enhancement are most commonly associated with multiple sclerosis (MS), and have been reported very rarely in NMOSD [4]. Histopathological analysis of a tumefactive lesion in a seropositive NMOSD patient reported by Tomizawa et al. demonstrated primary inflammatory demyelinating damage, which is usually found in MS. The presence of serum AQP4-IgG antibodies, the increased expression of AQP4 in the lesion, the closed-ring enhancement of the tumefactive lesion on MRI, and the observation of Creutzfeldt-Peters cells in histopathological examination, suggested a possible coexistence of NMOSD and MS. It was also speculated that the observed MS pathophysiology was secondarily caused by NMOSD attacks [2].

However, it is still unclear whether this phenomenon could be explained by the cytokine effect in the NMOSD pathophysiological process rather than by the coexistence of NMOSD and MS. In a postmortem study of an NMOSD case with extensive brain lesions, peripheral reactive astrocytes and intense macrophage activation were prominent simultaneously with the presence of partial axonal protection and complete demyelination. Unlike spinal cord lesions, cerebral lesions had little or no necrosis [5]. In our case, the presence of intense macrophage activation and myelin degradation demonstrated by MBP immunohistochemistry supported MS-like demyelination.

With the described histopathological evidence, ring or open-ring enhancing TDLs in NMOSD may suggest a new group of inflammatory demyelinating diseases. A potential B-cell and antibody-mediated process is suggested based on the clinical and radiological response to plasma exchange and rituximab treatments. Vasogenic oedema and macrophage-induced myelinolysis in TDLs might be a result of cytokine effect [6].

Based upon anecdote, rituximab is a recommended treatment option for TDLs, especially in cases resistant to high-dose steroids and plasma exchange therapy [7]. To the best of our knowledge, no case of NMOSD in which TDLs developed during rituximab treatment has previously been reported.

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