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CNS B cell infiltration in tumefactive anti-myelin oligodendrocyte glycoprotein antibody-associated disease

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Ryotaro Ikeguchi, Natsuki Kanda, Masaki Kobayashi, Kenta Masui, Masayuki Nitta, Tatsuro Misu, Yoshihiro Muragaki, Takakazu Kawamata, Noriyuki Shibata, Kazuo Kitagawa and Yuko Shimizu

Abstract

Background: Few studies have examined B cells among patients with anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD), including brain pathology.

Objective: To describe cases of tumefactive MOGAD with B-cell dominant central nervous system (CNS) infiltration.

Methods: In this study, we reviewed three cases with clinical and brain histopathological features with tumefactive MOGAD.

Results: Forty-nine cases of tumefactive brain lesions (TBL) between January 2003 and December 2023 were included; of these, seven had MOGAD. Three underwent a brain biopsy. B-cell dominant CNS infiltration was observed in two cases. In two cases with B-cell dominant CNS infiltration, symptoms included fever, headache, nausea, somnolence, and focal neurological deficits. Cerebrospinal fluid examination revealed both mild pleocytosis and negative oligoclonal IgG bands. Magnetic resonance imaging of the brain revealed large abnormal lesions extending from the basal ganglia to the parietotemporal lobe in both cases. These cases showed a good response to steroids; however, one case relapsed. Brain pathology showed demyelination and perivascular lymphocytic infiltration. One showed small vessel vasculitis. Deposition of the activated complement component was absent or rarely observed. Loss of MOG was observed in two cases.

Conclusion: MOGAD could exhibit B-cell dominant CNS infiltration and small vessel vasculitis. MOGAD should be considered in differential diagnosis of TBL.***Keywords:*** Anti-myelin oligodendrocyte glycoprotein antibody-associated disease, B cell, brain histopathology, brain tumor, myelin oligodendrocyte glycoprotein, tumefactive brain lesion

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Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a component of myelin protein expressed on the outer surface of the central nervous system (CNS) myelin sheath.[1] MOG is a long-studied representative autoantigen involved in experimental autoimmune encephalomyelitis, an animal model of inflammatory demyelinating disease (IDD). Studies have reported the detection of anti-MOG antibody (Ab) in several CNS IDDs, including neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), cortical encephalitis, myelitis, and optic neuritis.[2] These are called anti-MOG Ab-associated diseases (MOGAD); however, the detailed pathogenesis of MOGAD remains unclear.[2] For example, although an experimental study in mice has shown the pathogenicity of anti-MOG Ab, the pathogenicity in humans remains unknown.[3] Moreover, inflammatory demyelination and the presence of CD4+ T cells in brain lesions are pathological features of MOGAD.[4–18] However, only a few studies have examined B cells among patients with MOGAD,[19] including the corresponding brain pathology; hence, the role of B cells remains unclear.

In our previous studies, we focused on the differentiation between tumefactive brain lesions (TBL) and

Correspondence to:
Yuko Shimizu, Department of Neurology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
yuko.shimizu@twmu.ac.jp (yuko-sh@momo.so-net.ne.jp)

Ryotaro Ikeguchi, Natsuki Kanda, Masaki Kobayashi, Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan

Kenta Masui,
Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan

Masayuki Nitta,
Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Tatsuro Misu,
Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan

Yoshihiro Muragaki, Takakazu Kawamata,
Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Noriyuki Shibata,
Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan

Kazuo Kitagawa, Yuko Shimizu,
Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan

brain tumors, including glioma and lymphoma.[20] Although our previous long-term follow up revealed that TBL includes multiple sclerosis (MS), NMOSD, ADEM, vasculitis, and immunoglobin (IgG)4-related disease, we were unable to obtain a definitive diagnosis in more than 33% of patients with TBL. Interestingly, recent case reports and studies suggest that MOGAD is a newly recognized CNS disease that exhibits TBL.[6,9–11,14,21]

In this study, we report the cases of tumefactive MOGAD and their characteristic histopathological findings, including B-cell dominant CNS infiltration and vasculitis.

Methods

Participants

This retrospective study was conducted between January 2003 and December 2023 at the Tokyo Women's Medical University Hospital. Forty-nine patients with TBL were included, of whom seven were diagnosed with MOGAD and three underwent brain biopsy. During this period, a total of 15 patients had MOGAD, of which 8 had non-TBL MOGAD. All three patients underwent stereotactic brain biopsy during the acute and active phases. We defined TBL as lesions >2.0 cm in diameter on magnetic resonance imaging (MRI) of the brain, with mass effects and edema that mimicked CNS tumors.[22] Patients' clinical data and pathological findings are summarized in Table 1.

Assays for autoantibodies

As previously described, anti-MOG-Ab was detected using a live cell-based assay at the Tohoku University Graduate School of Medicine.[5] The positivity cut-off was 1:128.[2]

Brain biopsy

Brain tissues were obtained by stereotactic needle biopsy using a computer-navigated surgical system. Biopsy specimens were fixed in 20% formalin, dehydrated, and embedded in paraffin. Subsequently, multiple 6-μm-thick sections were deparaffinized, rehydrated, and used for hematoxylin-eosin, Klüver–Barrera, and immunohistochemical staining. Immunohistochemistry was performed using primary antibodies against the glial fibrillary acidic protein (diluted 1:1000; Dako, Glostrup, Denmark), neurofilament protein (diluted 1:5000; Covance), MOG (diluted 1:2000; Abcam, Cambridge, USA), oligodendrocyte transcription factor 2 (Olig2) (diluted 1:100; IBL, Minneapolis, MN, USA), complement C9neo (diluted 1:50; Hycult Biotech, Uden, the Netherlands), CD3 (diluted 1:100; Dako), CD4 (prediluted; Ventana Medical Systems, Tucson, AZ, USA), CD8 (diluted 1:50; Nichirei, Tokyo, Japan), CD20 (prediluted; Ventana Medical Systems), CD68 (diluted 1:10000; Clone KP-1; Dako), CD79a (diluted 1:50; Dako), CD138 (diluted 1:50; Dako), κ-chain (diluted 1:10; Dako), λ-chain (diluted 1:10; Dako), and Epstein–Barr virus-encoded early small RNA (EBER) (diluted 1:100; Dako). To visualize antibody binding, the researchers utilized the avidin-biotin-immunoperoxidase complex method, along with appropriate Vectastain ABC kits (Vector Laboratories, Burlingame, CA, USA), and 3,3'-diamonobenzidine tetrahydrochloride for chromogenic visualization. Background controls were generated for some sections by replacing primary antibodies with 3% skim milk or 3% nonimmune serum derived from the same animal species.

Standard protocol approvals, registrations, and patient consent

This study was approved by the Tokyo Women's Medical University School of Medicine Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data availability statement

Data are available on reasonable request.

Results

Case reports

Case 1. A 19-year-old male patient presented with dysarthria, left-sided hemiparesis, and hypoesthesia (Table 1). Despite the history of Wolff–Parkinson–White syndrome syndrome, he was healthy and not under any medication. There was no recent history of infection or vaccination. Brain MRI revealed high-intensity lesions on fluid-attenuated inversion recovery (FLAIR) in the bilateral thalamus with gadolinium contrast enhancement. Two weeks after onset, although glycerol was administered to reduce edema, the patient developed somnolence, anisocoria, left-sided ataxia, and dysuria. The right thalamic lesion spread to the parietotemporal lobe (diameter, 5.8 cm) and midbrain, showing patchy enhancement (Figure 1(a) and (b)). Methionine-positron emission tomography (PET) revealed abnormal methionine uptake in the right thalamic lesion, which suggested high-grade glioma or lymphoma (Figure 1(c)). A brain biopsy performed 3 weeks after onset showed demyelination and prominent B-cell dominant

Table 1. Clinical features of three patients with the tumefactive anti-MOG antibody-associated disease.

	Case 1	Case 2	Case 3
Clinical phenotype	MDEM with small vessel vasculitis	Multiple brain lesions without encephalopathy	Multiple brain lesions without encephalopathy
Sex	Male	Female	Male
Onset age (years)	19	15	22
Clinical manifestations	Dysarthria, hemiparesis, sensory dysfunction, somnolence, anisocoria, ataxia, and dysuria	Headache, fever, nausea, and hemiparesis	Headache, visual field deficit, and facial palsy
Serum anti-MOG ab titer at onset (serum)	512	128	1024
CSF findings			
Pleocytosis	+	+	+
OCB	−	−	+
Brain MRI findings	Bilateral thalamus (right dominant, max. diameter 5.8 cm), parietotemporal lobe, and midbrain with patchy enhancement	Left basal ganglia (caudate nucleus and putamen), parietotemporal lobe (max diameter 6.2 cm) with marginal enhancement	Left basal ganglia, temporal lobe (max diameter 4.8 cm) with open-ring enhancement
Relapse	+	+	+
EDSS at last follow-up	3	0	0
Brain pathology			
Demyelination	+	+	+ (actively demyelinating lesion)
Perivascular lymphocytic infiltration	+ (small vessel vasculitis)	+	+
Infiltrating lymphocytes in the perivascular lesion	B cell >> T cell	B cell > T cell	T cell > B cell
Macrophage/ Microglia	+	+	+
Astrogliosis	+	+	+
Axonal loss	Preserved	Preserved	Preserved
MOG loss	+	+	+
Complement deposition	±	±	±

CSF: colony stimulating factor; EDSS: Expanded Disability Status Scale; MDEM: multiphasic disseminated encephalomyelitis; MOG: myelin oligodendrocyte glycoprotein; MRI: magnetic resonance imaging; OCB: oligoclonal IgG band.

perivascular lymphocytic infiltration in the demyelinating lesion (Figure 1(d)–(k)), suggesting B-cell lymphoma. However, there were no pathological findings that supported the diagnosis of lymphoma, including monoclonality or Epstein–Barr virus positivity (Figure 1(l)–(n)). Moreover, the structures of several small blood vessel walls were disrupted, as accompanied by lymphocytic infiltration in blood vessels, suggesting

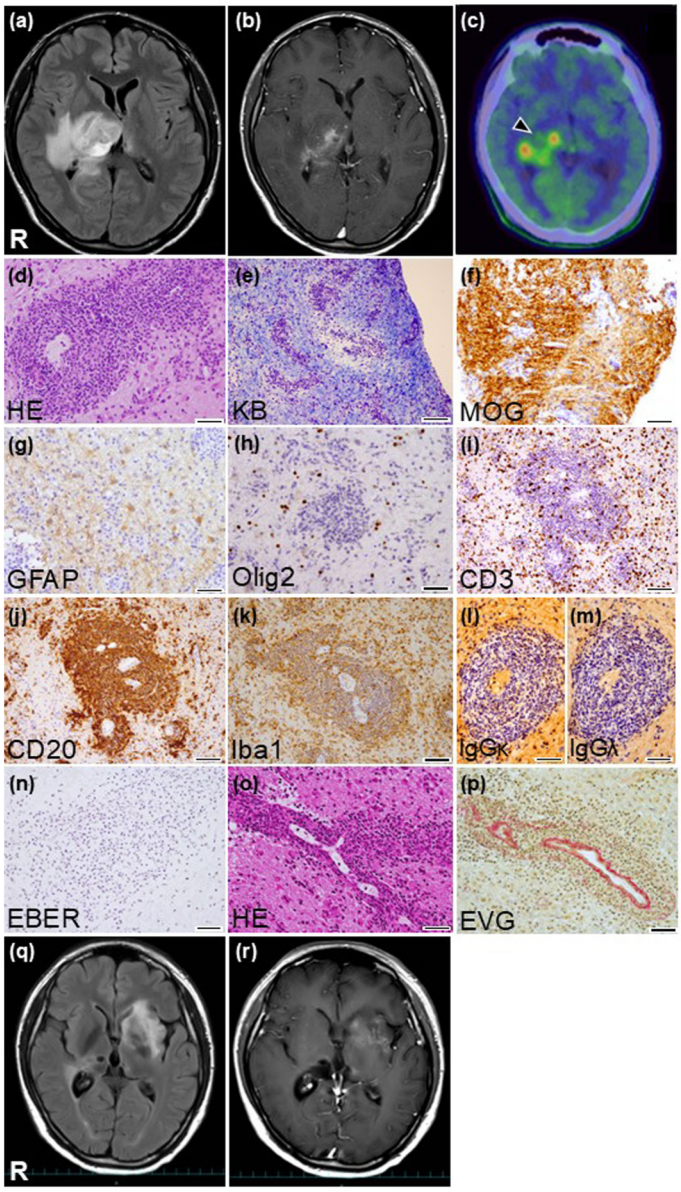

Figure 1. Brain imaging ((a)–(c)) and histopathological findings ((d)–(p)) of case 1. (a) FLAIR imaging reveals tumefactive high-intensity lesions from the right thalamus to the parietotemporal lobe. A midline shift is observed. (b) T1-weighted imaging after gadolinium enhancement shows patchy enhancement. (c) Methionine-PET reveals a high methionine uptake (maximum standardized uptake value, 4.3; target-to-normal tissue ratio, 3.4) in the lesion (arrowhead). (d) HE staining shows prominent perivascular lymphocytic infiltration. (e) KB staining shows perivascular demyelination. (f) The staining for MOG shows a loss of MOG immunoreactivity in the perivascular lesion. (g) GFAP staining shows reactive gliosis. (h) Olig2 staining shows immunoreactivity in the nuclei of oligodendrocytes. The immunohistochemistry for CD3 (i) and CD20 (j) reveal T- and B-cell infiltrates around the vessels. Infiltrating lymphocytes are B-cell dominant. (k) Iba-1 positive microglia are observed. No significant monoclonality of λ light chain (l) or κ light chain (m) is observed. (n) The result of *in situ* hybridization for Epstein–Barr virus-encoded early small RNA (EBER) is negative. HE staining (o) and EVG staining (p) shows the disruption of several blood vessel walls. (q) FLAIR imaging reveals high-intensity lesions extending from the left basal ganglia to the insula 4.5 years after onset. (r) T1-weighted imaging after gadolinium enhancement shows heterogeneous enhancement. Scale bars in (d), (e), (f), (g), (h), (l), (m), (n), (o), and (p) = 50 μm. Scale bars in (i), (j), and (k) = 100 μm. EVG: Elastica van Gieson; FLAIR: fluid-attenuated inversion recovery; GFAP: glial fibrillary acidic protein; HE: hematoxylin-eosin; Iba-1: ionized calcium-binding adapter molecule 1; KB: Klüver-Barrera; MOG: myelin oligodendrocyte glycoprotein; NFP: neurofilament protein; Olig2: oligodendrocyte transcription factor 2; PET: positron emission tomography.

small-vessel vasculitis (Figure 1(o) and (p)). Routine laboratory tests, including serum collagen disease and vasculitis markers, infectious markers including tuberculosis, and tumor markers, were normal, and anti-AQP4 Ab was absent. A CSF analysis revealed mononuclear pleocytosis (41.3/μL), negative oligoclonal IgG bands (OCBs), and normal levels of lymphoma markers, including soluble interleukin-2 receptor and interleukin-10. Polymerase chain reaction test results for herpes simplex virus, varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus were negative. The bacterial culture test was negative. The patient was suspected of small vessel CNS vasculitis. However, in addition to the absence of fibrin deposition and/or necrosis, serum anti-MOG Ab was positive, with a titer of 1:512; thus, a diagnosis of MOGAD was made.[2] The patient was treated with pulse steroids followed by oral prednisolone. Although there were no neurological symptoms, abnormal subcortical lesions in the left frontal lobe and right temporal lobe were detected in a follow-up brain MRI, 3 years after onset (when taking 11 mg/day of prednisolone). Another follow-up brain MRI revealed an abnormal lesion extending from the left basal ganglia to the insula with heterogeneous enhancement 4.5 years after onset (when taking 10 mg/day of prednisolone) (Figure 1(q) and (r)). Serum anti-MOG Ab test results were negative, respectively. The patient was treated with pulse steroids, followed by oral prednisolone. We administered ofatumumab (anti-CD20 monoclonal antibody). Subsequently, relapse or the appearance of new abnormal lesions in the brain was not observed. The patient showed permanent sequelae (EDSS score, 3.0) at the last visit (5.5 years after onset).

Case 2. A 15-year-old female patient presented with a headache, fever, nausea, and right hemiparesis (Table 1). She was healthy and required no medications. Brain MRI revealed high-intensity lesions on FLAIR in the left basal ganglia (caudate nucleus and putamen) to the parietotemporal lobe (diameter, 6.2 cm), with marginal enhancement (Figure 2(a) and (b)). Methionine-PET revealed abnormal methionine uptake in the left basal ganglia, suggesting a high-grade glioma (Figure 2(c)). A brain tumor was suspected, and a biopsy was performed 3 weeks after onset. Before the brain biopsy, glycerol and an intravenous corticosteroid were administered to reduce edema. The histopathological findings showed demyelination and perivascular B-cell dominant lymphocytic infiltration in the demyelinating lesion (Figure 2(d)–(l)). Routine laboratory tests were normal, including serum collagen disease and vasculitis markers, infectious and tumor markers. A CSF analysis revealed mononuclear pleocytosis (77.7/μL) and negative OCBs. Clinical findings suggested a demyelinating disease of the CNS without encephalopathy. Serum anti-MOG Ab was positive with a titer of 1:128, whereas anti-AQP4 Ab was absent; thus, a diagnosis of MOGAD was made.[2] The neurological symptoms gradually improved after oral prednisolone administration. Nine months after biopsy, the patient presented with a headache, and a brain MRI revealed new abnormal lesions in the pons (Figure 2(m) and (n)) and right temporal lobe with marginal enhancement (oral prednisolone 2 mg/day). Serum anti-MOG Ab levels were negative during relapse. The patient was treated with pulse steroids followed by oral prednisolone. There was no relapse for 6 years after the last relapse without sequelae.

Case 3. A 22-year-old male patient presented with headache, visual field deficits, and right facial palsy (Table 1). He was healthy and required no medications. Brain MRI revealed high-intensity lesions on FLAIR in the left basal ganglia to the parietotemporal lobe (diameter, 4.8 cm) with open-ring enhancement (Figure 3(a) and (b)). A brain tumor was suspected, and a biopsy was performed 3 weeks after onset. Before the brain biopsy, glycerol and an intravenous corticosteroid were administered to reduce edema. Histopathological results showed prominent demyelination and perivascular lymphocytic infiltration in the demyelinating lesion (Figure 3(c)–(k)). Routine laboratory tests were normal, including serum collagen disease, vasculitis markers, and infectious and tumor markers. A CSF analysis showed mild mononuclear pleocytosis (18.7/μL) and positive OCBs. Clinical findings suggested ADEM without encephalopathy. Serum anti-MOG Ab was positive with a titer of 1:1,024, whereas anti-AQP4 Ab was absent; thus, MOGAD was diagnosed.[2] Neurological symptoms spontaneously improved, and oral corticosteroids were initiated and tapered. Although there were no new neurological symptoms, a follow-up brain MRI detected new abnormal lesions in the right occipital lobe (Figure 3(l) and (m)), parietal lobe, and left temporal lobe with ring-like enhancement 6 months after brain biopsy (oral prednisolone, 10 mg/day). Serum anti-MOG Ab was positive with a titer of 1:2048 at relapse. The patient was treated with pulsed steroids, resulting in full recovery. Thereafter, prednisolone was continued. There was no relapse for 5.5 years after the last relapse without sequalae.

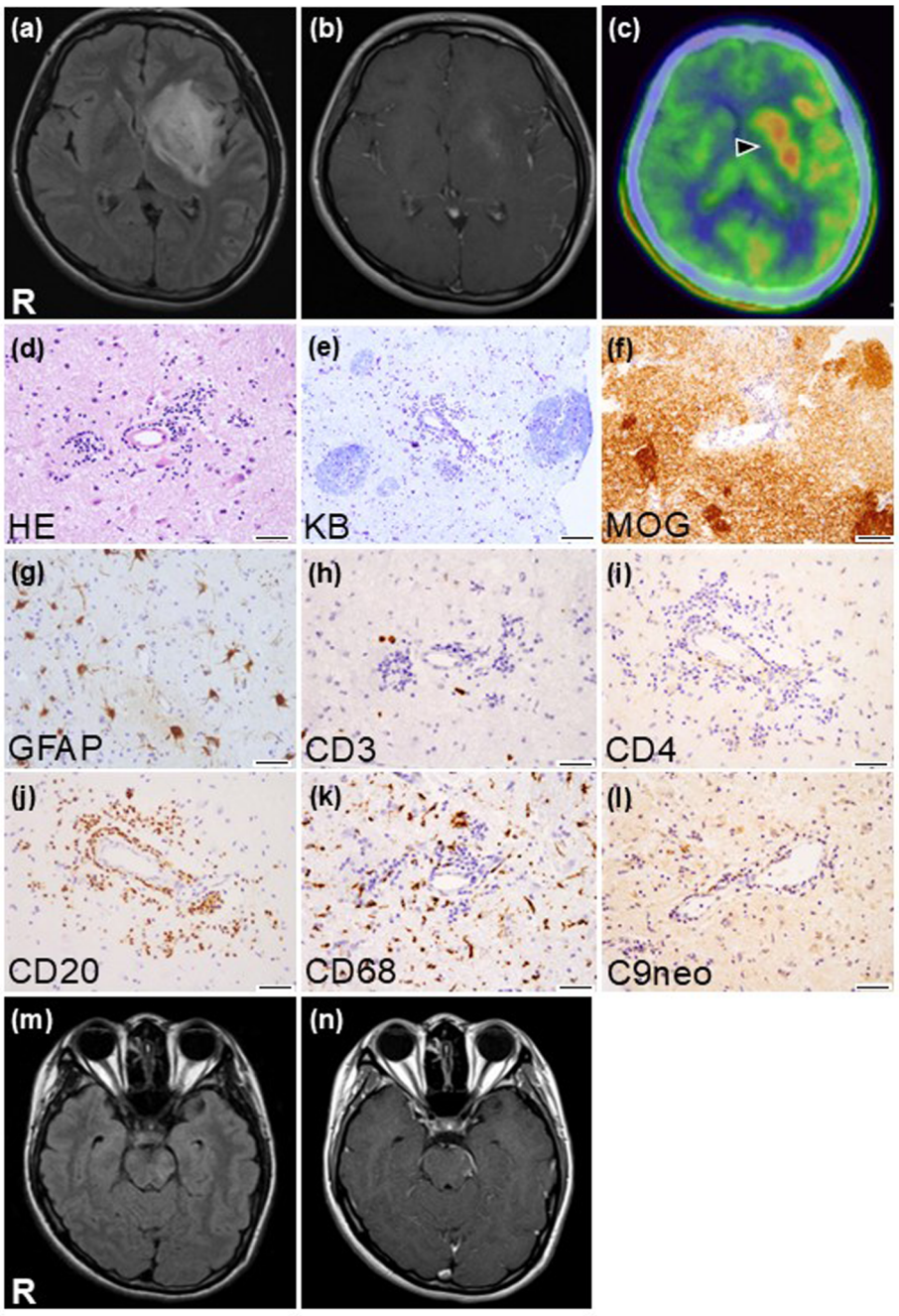

Figure 2. Brain imaging ((a)–(c)) and histopathological findings ((d)–(l)) of case 2. (a) FLAIR imaging reveals a tumefactive high-intensity lesion from the left basal ganglia (caudate nucleus and putamen) to the parietotemporal lobe. (b) T1-weighted imaging after gadolinium enhancement shows marginal enhancement. (c) Methionine PET reveals a high methionine uptake (maximum standardized uptake value, 2.5; target-to-normal tissue ratio, 2.2) in the lesion (arrowhead). (d) HE staining shows perivascular lymphocytic infiltration. (e) KB staining shows perivascular demyelination. (f) Staining for MOG shows a loss of MOG immunoreactivity in the perivascular lesion. (g) GFAP staining shows reactive gliosis. ((h)–(j)) Immunohistochemistry for CD3 (h), CD4 (i), and CD20 (j) reveal both T- and B-cell infiltrates around the vessels. Infiltrating lymphocytes are B-cell dominant. (k) CD68-positive macrophages are also observed in the perivascular lesion. (l) Deposition of the activated complement component (C9neo) is rarely observed. (m) FLAIR imaging reveals a high-intensity lesion in the pons 9 months after brain biopsy. (n) T1-weighted imaging after gadolinium enhancement shows marginal enhancement. Scale bars in (d), (f), (g), (h), (i), (j), (k), and (l) = 50 μm. Scale bar in (e) = 100 μm. FLAIR: fluid-attenuated inversion recovery; GFAP: glial fibrillary acidic protein; HE: hematoxylin-eosin; FLAIR: fluid-attenuated inversion recovery; KB: Klüver-Barrera; MOG: myelin oligodendrocyte glycoprotein; PET: positron emission tomography.

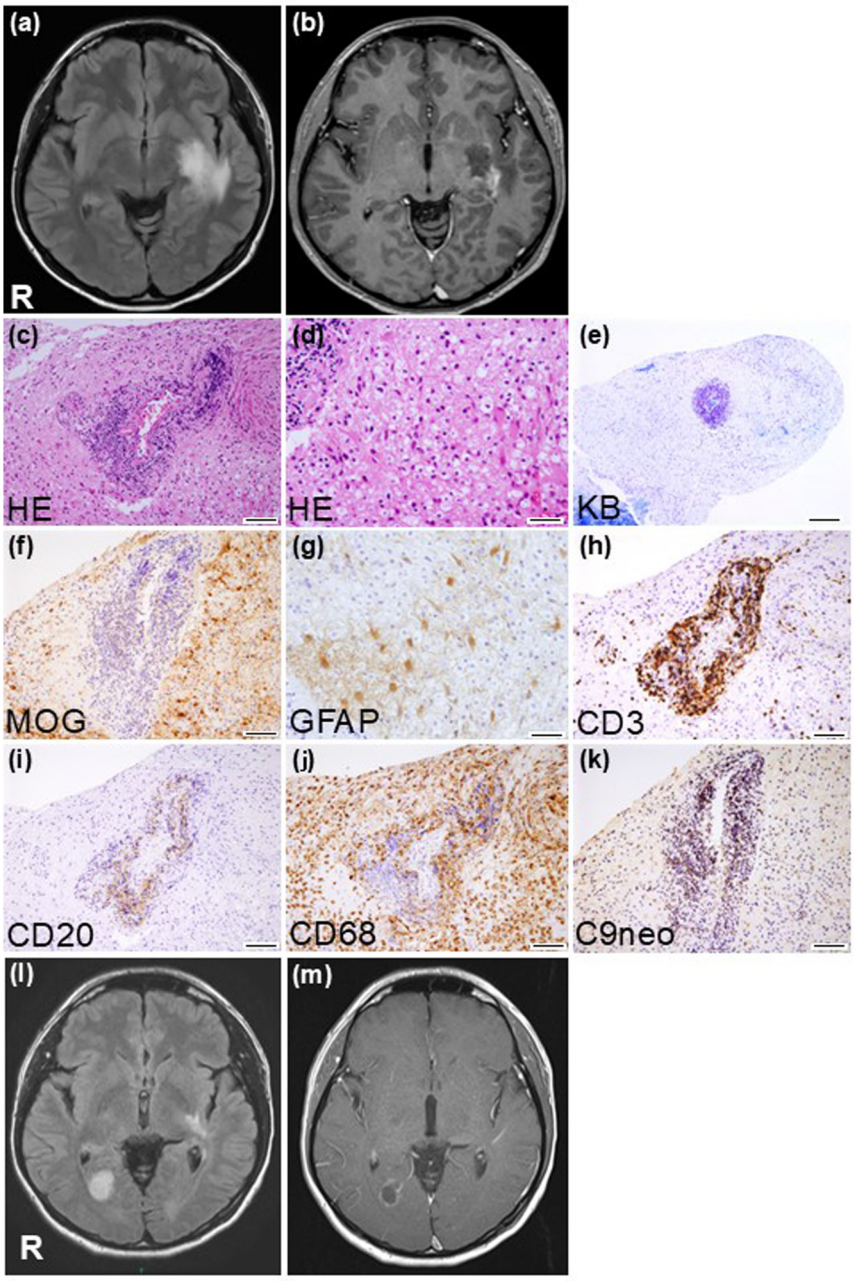

Figure 3. Brain imaging ((a), (b), (m), and (n)) and histopathological findings ((c)–(l)) of case 3. (a) FLAIR imaging reveals a tumefactive high-intensity lesion from the left basal ganglia to the parietotemporal lobe. (b) T1-weighted imaging after gadolinium enhancement shows open-ring enhancement. (c) and (d) HE staining reveal perivascular lymphocytic infiltration (c) and marked foamy macrophages (d). (e) KB staining shows prominent demyelination. (f) The staining for MOG shows a loss of MOG immunoreactivity in the perivascular lesion. (g) GFAP staining shows reactive gliosis. (h) and (i) Immunohistochemistry for CD3 (h) and CD20 (i) reveal both T- and B-cell infiltrates around the vessels. Infiltrating lymphocytes are T-cell dominant (compatible CD4 + and CD8+ T cells). (j) CD68-positive macrophages are observed in the perivascular lesion. (k) Deposition of the activated complement component (C9neo) is rarely observed in the perivascular lesion. (l) FLAIR imaging reveals a high-intensity lesion in the right occipital lobe 6 months after brain biopsy. (m) T1-weighted imaging after gadolinium enhancement shows a ring-like enhancement. Scale bars in (c), (d), and (g) = 50 μm. Scale bars in (f), (h), (i), (j), and (k) = 100 μm. Scale bars in (e) = 200 μm. FLAIR: fluid-attenuated inversion recovery; GFAP: glial fibrillary acidic protein; HE: hematoxylin-eosin; FLAIR: fluid-attenuated inversion recovery; KB: Klüver-Barrera; MOG: myelin oligodendrocyte glycoprotein; PET: positron emission tomography.

Brain pathology

Histopathological findings revealed inflammatory demyelinating lesions with reactive astrocytic gliosis in all three cases (Figures 1–3 and Table 1). Axons were relatively preserved. Myelin-laden macrophages were present at the demyelinating and perivascular lesions. MOG immunoreactivity was sparse and diminished in the demyelinating lesions (Figures 1(e), 2(e), and 3(f)). Lymphocytic infiltration was perivascular in all cases (Figures 1(d), 2(d), and 3(c)). Case 1 demonstrated disruptions of small blood vessel walls accompanied by lymphocytic infiltration in blood vessel walls, suggesting small vessel vasculitis; there was no evident fibrin deposition and/or necrosis (Figure 1(o) and (p)). Moreover, infiltrative lymphocytes were B-cell dominant (numerous CD20 + CD79a + B cells were observed in the perivascular lesion) (Figure 1(j)). Even in case 2, infiltrative lymphocytes were B-cell dominant; moderate CD20 + CD79a + B cells were observed in the perivascular lesion (Figure 2(j)). In case 3, the degree of demyelination was prominent and numerous foamy macrophages containing myelin debris were observed (Figure 3(d) and (e)). Infiltrative lymphocytes were T-cell dominant (i.e. compatible with CD4 + and CD8+ T cells) (Figure 3(h) and (i)). These were consistent with "actively demyelinating lesions" observed in patients with classical MS.[23,24] CD138 + plasma cells were rarely detected in these three cases. Deposition of the activated complement component was absent or rarely seen in demyelinating lesions in all cases (Figure 2(l) and 3(k)). In case 1, lymphoma was strongly suspected due to the prominent aggregation of B cells; therefore, we studied the EBER, IgG lambda, IgG kappa, MIB-1, Ki-67, and other tumor markers. However, these examinations did not reveal any evidence of lymphoma (Figure 1(l)–(n)).

Discussion

This study showed that the characteristics of the brain histopathology of MOGAD were variable; however, demyelination, perivascular lymphocytic infiltration, reactive astrogliosis, and relatively preserved axons are common pathological findings in MOGAD,[4–18] and B-cell dominant lymphocytic infiltration and small vessel vasculitis could be found in the brain lesion.

While most previous studies and case reports showed that infiltrative lymphocytes were CD4+ T cells dominant in demyelinating lesions,[4–17] cases 1 and 2 in the present study showed perivascular B-cell dominant CNS infiltration. Particularly, prominent B-cell infiltration was noted in case 1. In addition, only one case report showed B-cell dominant infiltration.[18] Generally, few CNS diseases show B-cell dominant lymphocytic infiltration in the CNS. For example, B-cell lymphoma is categorized as such, and MS is representative of B-cell accumulative CNS disease. Among patients with MS, B and CD8+ T cells are dominant (CD8+ T cells > B cells) in the CNS throughout the course of the disease.[25] Prominent B-cell infiltrations were the highest in a subset of cases with the most active disease and lesions in patients with MS. Remarkable B-cell aggregation, called "ectopic B-cell follicle," is specifically observed in patients with secondary progressive MS.[26] Patients with ectopic B-cell follicles in MS showed several characteristics, including a younger age at MS onset, a more severe disease course, and more pronounced demyelination, suggesting ectopic B-cell follicles related to the severity and activity of MS.[26] These and the efficacy of B-cell depleting therapy also suggest the pathogenicity of B-cells among patients with MS. In fact, rituximab (anti-CD20 monoclonal Ab that deletes B cells in the blood) significantly reduces relapse even in patients with MOGAD.[27–29] These suggest the pathogenicity of B cells in MOGAD, however, there is a paucity of studies examining B cells in patients with MOGAD, and the pathogenesis of B-cells in patients with MOGAD remains unclear. The present case (case 1) with prominent B cell infiltration showed large lesions (maximum diameter >5.0 cm) and had permanent sequelae. Therefore, we speculate that CNS B-cell dominant CNS infiltration may be correlated with high disease activity and severity, even among patients with MOGAD. As mentioned above, only one case report reported B-cell dominant infiltration in the CNS of MOGAD.[18] This case is a 35-year-old female with cortical encephalitis. Brain biopsy showed marked meningeal inflammation, extensive macrophage/microglial reactivity in both meninges and cortex, and extensive subpial cortical inactive demyelination. In addition, focal meningeal CD20+ B-cell abundant aggregates, which were inconsistent with ectopic B-cell follicles found in MS,[26] were observed. While there is no apparent similarity between present cases and this reported case other than being MOGAD, it seems that different subtypes of MOGAD (cortical encephalitis) can exhibit B-cell predominant lymphocytic infiltration into the brain.

The roles of B cells among patients with CNS IDDs are speculated to be as follows: (1) production of Abs, (2) antigen presentation as an antigen-presenting cell (APC), and (3) production of inflammatory cytokines (interleukin-6, granulocyte macrophage-CSF

(GM-CSF), and tumor necrosis factor-α).[30–32] An anti-MOG Ab from patients with MOGAD showed pathogenicity to oligodendrocytes based on *in vitro* and *in vivo* experiments,[33,34] as well as persistent anti-MOG Ab positivity correlated with recurrent disease course.[2] Furthermore, some patients with MOGAD showed positivity for anti-MOG Ab only in their CSF, indicating the intrathecal production of anti-MOG Ab.[35] Therefore, we speculate that MOG-specific B cells in the CNS may differentiate and mature into anti-MOG Ab-producing B cells and/or plasmablasts in MOGAD. In patients with MS and NMOSD, B cells are considered as an APC.[31,36] In patients with MOGAD, the frequency of MOG-specific B cells increased in peripheral blood, and this subset can present antigens to T cells at concentrations 10^{3-} to 10^{4-} fold lower than that by nonspecific B cells or monocytes.[19,37] Although no studies have proved B-cell APC function in the CNS of patients with MOGAD, our present study and previous studies suggest that CNS B cells may play a pathogenic role as an APC; thus, further studies are required to elucidate this matter. Moreover, CSF levels of interleukin-6, interferon-γ, and GM-CSF increased in patients with MOGAD compared with those in patients with MS,[38] suggesting that B cells may contribute to these increased inflammatory cytokines in the CNS. Interleukin-6 levels in the CSF increased, even in the present three cases in the acute phase (data not shown).

Similar to case 1 in this study, CNS vasculitis has been reported in six other patients in previously published case reports of MOGAD.[12,13,15,17] The mean age at onset in these cases was 26.2 (mean, 5–60) years, and 4 patients were male. CSF analysis showed pleocytosis in all cases. In four cases, the brain MRI revealed a cortical lesion.[12,15] Although brain histopathology revealed perivascular lymphocytic infiltration in all cases, there was no evidence of demyelination in two cases.[13,15] None showed B-cell dominant lymphocytic infiltration. A previous study reported seven cases with younger onset (<18 years) biopsy-proven small vessel primary angiitis of the CNS.[17] Two of the seven cases were discovered to have anti-MOG Abs. These previous and present studies suggest that MOGAD could show CNS vasculitis, and part of them may lack evidence of demyelination, which is a typical pathological finding for MOGAD.

We speculate that the autoimmune mechanisms of MOGAD in the brain are as follows: First, unknown triggers activate autoimmunity and induce blood–brain barrier damage. Activated T cells (particularly CD4+) and B cells migrate to the CNS. Anti-MOG Abs produced in the blood also migrate to the CNS during this phase. These lymphocytes and anti-MOG Abs interact in the CNS (B cells may present antigens to CD4+ T cells and produce inflammatory cytokines). Subsequently, CD4+ T cells are activated in the CNS. Activated MOG-specific B cells may differentiate and mature into anti-MOG Ab-producing B cells and/or plasmablasts; these cells also produce anti-MOG Abs in the CNS. Consequently, demyelination occurs by macrophages with or without the involvement of the complement system.

The brain tumor was suspected in the present three cases because of a large brain lesion (maximum diameter, > 5.0 cm) with an edema and/or mass effect. In addition to gadolinium enhancement on MRI, the two cases showed abnormal methionine uptake on methionine-PET, suggesting malignant brain tumors, including high-grade glioma or lymphoma (Figures 1(c) and 2(c)). However, the rapid progression of neurological symptoms and good response to steroids in the present cases were more typical for IDDs than for brain tumors. Moreover, a young onset is not typical of lymphoma. There were 49 patients with TBL, including the present three cases in our cohort. Among them, seven patients (14%) were finally diagnosed with MOGAD. Clinical presentation included MDEM (n = 1, case 1), multiple brain lesions without encephalopathy (n = 4, cases 2 and 3), encephalitis (n = 1), and NMOSD (n = 1). The other patients with TBL were finally diagnosed with MS, ADEM, drug-related demyelinating syndromes, primary CNS vasculitis, and IgG4-related disease in our cohort. In three cases, histopathological results showed demyelination and perivascular lymphocytic infiltration in the demyelinating lesion. MOG immunoreactivity was also diminished in the demyelinating lesion. These pathological findings are consistent with the results of previous studies and case reports of MOGAD. Recently, a study reported the clinical characteristics of tumefactive MOGAD, NMOSD, and MS.[21] First, the frequency of TBL in MOGAD (22%) was higher than that in NMOSD and MS. Tumefactive MOGAD cases exhibited more somnolence and headache compared to tumefactive NMOSD and MS cases. Additionally, CSF analysis revealed less frequent positive OCBs in MOGAD than in MS and a higher median white cell count in MOGAD than in MS. Regarding brain MRI, diffusion-weighted imaging (DWI) restriction was rarely observed in MOGAD. Although mild DWI restriction was observed in case 1, neurological

symptoms (somnolence in case 1, headache in cases 2 and 3) and CSF findings (pleocytosis in 3 cases and negative OCBs in 2 cases) were consistent with tumefactive MOGAD. Furthermore, in the present cases, the presence of deep gray matter lesions (thalamus in case 1, caudate nucleus and putamen in case 2, and putamen in case 3) also suggested MOGAD.[2,21] These results suggest that MOGAD is an important differential diagnosis of TBL.[6,9–11,14,21]

This study has some limitations. First, the sample size was small. Second, in case 1, the biopsy samples were limited, resulting in some panels in the figures not being consecutive sections. Third, corticosteroids suppress the function of both T and B cells, mainly suppressing T cells.[39] Therefore, using corticosteroids before brain biopsy may have influenced the findings of brain pathology (B-cell dominant lymphocytic infiltration). However, although corticosteroid treatment was administered before the brain biopsy in case 3, CNS infiltrating lymphocytes were T-cell predominant. It is unclear how corticosteroids affect the distribution of infiltrating lymphocytes in the brain. In case 1, corticosteroids were not administered before the brain biopsy due to the suspicion of malignant lymphoma. Corticosteroid therapy temporarily reduces CNS lymphoma-associated lesions and delays lymphoma diagnosis. However, if signs of brain herniation due to brain edema are suspected, the use of corticosteroids for reducing edema should be considered. Fourth, some T cells express CD20, a representative marker of B cells.[40] We considered that some CD20 + lymphocytes might be CD20+ T cells. Therefore, we stained the cells for CD79a, which has a higher specificity for B cells than CD20. Consequently, we found that most perivascular CD20 + lymphocytes expressed CD79a. Therefore, we concluded that most of these infiltrating lymphocytes are B cells. Finally, given the small number of cases, less than typical clinical presentation of MOGAD in some of the cases, and low positive serum anti-MOG Ab titer (1:128) in case 2, the possibility of false positive cannot be ruled out.[2,41] In addition, anti-MOG Abs has been reported positive in a case with malignant lymphoma previously.[42] In this case, dramatic improvement was observed temporarily with steroid treatment. In malignant lymphoma, some cases show temporary improvement with immunotherapies effective for MOGAD, such as steroids and anti-CD20 monoclonal antibody. Additionally, patients with malignant lymphoma can experience temporary spontaneous remission.[43] Therefore, careful attention is needed to differentiate MOGAD from malignant lymphoma.

In conclusion, the present study showed that MOGAD could exhibit various histopathological findings, including B-cell dominant CNS infiltration and small vessel vasculitis. Although the histopathological findings of MOGAD are heterogeneous, demyelination and perivascular lymphocytic infiltration are common. Additionally, MOGAD is an important differential diagnosis for TBL. Further studies are required to elucidate the pathogenesis of MOGAD in detail.

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Authors' contributions

RI contributed to the study design, literature research, data acquisition, pathological analysis, and manuscript drafting. NK contributed to the study design, literature research, data acquisition, and manuscript drafting. MK contributed to the data acquisition, pathological analysis, and manuscript review. KM and NS contributed to the data acquisition and pathological analysis. MN contributed to the data acquisition. TM contributed to the pathological analysis. YM, TK contributed to the data acquisition. KK contributed to the critical revision of the manuscript for intellectual content. YS contributed to the study design, data acquisition, and manuscript revision.

Declaration of conflicting interests

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ORCID iDs

Ryotaro Ikeguchi https://orcid.org/0000-0002-1197-1705
Yuko Shimizu https://orcid.org/0000-0002-1903-1400

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