Anti-Aquaporin-4 Antibody-Seronegative NMO Spectrum Disorder with Baló’s Concentric Lesions

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Abstract

A 34-year-old woman developed simultaneous bilateral severe optic neuritis and subsequent myelitis. Two months after the first attack, she developed a headache and dysesthesia in the left arm. Brain magnetic resonance imaging revealed multiple hyperintense lesions in the white matter of the right hemisphere, some of which were Baló-like concentric lesions. Our diagnosis was neuromyelitis optica spectrum disorder with Baló’s concentric sclerosis (BCS), although the patient was negative for anti-aquaporin-4 (anti-AQP4) antibodies. Our case suggests that Baló’s concentric sclerosis overlaps with neuromyelitis optica spectrum disorder and that this overlapping is caused by a mechanism that does not involve anti-AQP4 antibodies.

Key words: Baló’s concentric sclerosis, neuromyelitis optica, aquaporin-4, multiple sclerosis, myelitis, optic neuritis


Introduction

Neuromyelitis optica (NMO) is a severe demyelinating disease defined principally by its tendency to selectively affect optic nerves and the spinal cord causing recurrent attacks of blindness and paralysis. Anti-aquaporin-4 (anti-AQP4) antibodies have been found to be a specific biomarker for NMO, and it was also discovered that NMO-IgG recognizes the astrocytic water channel aquaporin-4 [AQP4 (1, 2)]. Some clinically limited forms of this disorder, such as bilateral simultaneous or recurrent optic neuritis, are included in its pathogenetic spectrum and are classified as NMO spectrum disorder (NMOsd) (3).

Meanwhile, Baló’s concentric sclerosis (BCS) is a rare demyelinating disorder pathologically characterized by alternating layers of myelinated and demyelinated tissue (4). It has been pointed out that NMO and BCS have some features in common (5), and cases of NMO (Devic’s syndrome) with Baló’s concentric lesions (BCLs) have been reported (6). However, such cases were reported a long time before the disease entity of NMO was established (1, 7, 8).

Recently, a case of NMO with a BCL in the brainstem was reported (9). In addition, a loss of APQ4 in BCLs and a lack of anti-AQP4 antibodies were reported in a pathological study (10, 11), thus resulting in more attention to the associations between NMO and BCL and between BCS and APQ4. We herein describe a case of NMOsd without anti-AQP4 antibodies with BCLs. Our case may help to further understanding of the associations between NMO, BCS/BCL and APQ4.

Case Report

A 34-year-old Japanese woman with no prior neurologic history presented with bilateral simultaneous optic neuritis in April 2010. The patient was admitted one week after symptom onset. A neurological examination revealed no abnormalities, except for bilateral visual acuity loss. The next day, the patient developed sensory disturbances at the T7 spinal segment. Brain magnetic resonance imaging (MRI) revealed bilateral tortuous swelling of the optic nerves on fluid-attenuated inversion recovery (FLAIR) images (Figure A). No abnormalities fulfilling Barkhof’s criteria (12)
were observed. MR T2-weighted imaging of the spinal cord revealed centrally located and longitudinal lesions extending from the T5 to T7 vertebral segments (Figure B, C). Axial T2-weighted MRI of the T6 vertebral segment also revealed Baló-like lesions with concentric rings (Figure B). The patient was also diagnosed with transverse myelitis because she exhibited bilateral symptoms at a clearly defined sensory level (13). Common biochemical laboratory tests were normal. The level of anti-APQ4 antibodies was tested as previously reported (14), and a serum sample obtained nine days after the neurologic onset was negative. Antinuclear, anti-neutrophil cytoplasmic, anti-SSA/RO, anti-SSB/LA and antiphospholipid antibodies were also negative. The patient was admitted two courses of intravenous methylprednisolone pulse therapy at a dose of 1,000 mg for three consecutive days followed by oral prednisolone at a dose of 15 mg on alternate days, after which her symptoms improved.

In June 2010, she was readmitted to the hospital due to a headache and left dysesthesia in the left arm. A neurological examination revealed left facial weakness, hemiparesis and sensory disturbances on the left side of the body. T2-weighted MRI and FLAIR imaging of the brain revealed multiple hyperintense lesions in the white matter of the right hemisphere, some of which were Baló-like concentric lesions with various rings (Figure D). The central cores of these lesions demonstrated hyperintensity on diffusion-weighted imaging (DWI) (Figure E); however, no abnormalities in the apparent diffusion coefficient (ADC) were observed (Figure F). The intervening rings exhibited relatively unrestricted diffusion. As previously reported (15), the outermost layer demonstrated hyperintensity on DWI with a restricted ADC and revealed an active demyelination site on gadolinium enhancement. A cerebrospinal fluid analysis revealed a normal white blood cell count and protein level with mild elevation of the level of myelin basic proteins (183 pg/mL; normal limit, <102 pg/mL). No oligoclonal bands were observed and the IgG index was normal. A test for anti-APQ4 antibodies performed one day after the onset of the second neurologic episode was also negative. Intravenous methylprednisolone pulse therapy at a dose of 1,000

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**Figure.** MRI of the present patient with neuromyelitis optica spectrum disorder and Baló’s concentric lesions. Brain MRI fluid-attenuated inversion recovery (FLAIR) imaging performed after the first episode revealed bilateral tortuous swelling of the optic nerves (A). Spinal cord MRI performed after the first episode revealed centrally located, concentric lesions at the T6 vertebral segment on axial T2*-weighted imaging (B) and longitudinal lesions extending more than two vertebral segments on sagittal T2-weighted imaging (C). Brain MRI performed after the second episode revealed concentric lesions comprising the central core and various rings in the white matter on FLAIR imaging (D), diffusion-weighted imaging (E) and apparent diffusion coefficient imaging (F). MRI FLAIR imaging revealed a remarkable reduction in the size of the lesions following steroid treatment compared with that observed before treatment (G).
mg for three consecutive days was reinitiated. Following the administration of pulse therapy, oral prednisolone at a dose of 40 mg daily was given, reduced by 5 mg every four weeks, then stopped. The patient’s symptoms remarkably improved, with the exception of residual, mild left hemiparesis, left facial weakness, sensory disturbances of the left side of the body and decreased visual acuity. MRI revealed a remarkable reduction in the size of the lesions following steroid therapy (Figure G). The patient remains free of relapse more than nine months after the onset of the second episode.

**Discussion**

This case report describes a patient with simultaneous bilateral optic neuritis, transverse myelitis and Baló’s concentric lesions.

NMO-IgG and anti-AQP4 antibodies, biomarkers of NMO (1, 2), are also detected in the serum of patients with NMO-related disorders (3). Any syndrome that includes recurrent or simultaneous bilateral optic neuritis or single or recurrent myelitis associated with longitudinally extensive myelitis of more than three vertebral segments is referred to as NMOsd in the context of this study (3). The patient did not fulfill the criteria for NMO due to the negative test results for NMO-IgG/anti-AQP4 antibodies and the presence of myelitis shorter than three vertebral segments. However, she originally presented with simultaneous bilateral severe optic neuritis, immediately followed by transverse myelitis, the typical clinical course of NMO. In addition, brain MRI showed no abnormalities fulfilling Barkhof’s criteria (12), and spinal cord MRI revealed long lesions extending more than two vertebral segments. The spinal cord lesions observed in patients with MS are rarely longer than a single vertebral segment (16). Hence, the patient was diagnosed with NMOsd, although the differential diagnoses, including acute disseminated encephalomyelitis and tumefactive MS, could not be completely excluded.

The association between BCS and NMO has hardly been discussed due to differences in the clinical and laboratory references are indicated by the superscript numbers in parentheses.

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<td>+</td>
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<td>-</td>
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<tr>
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<td>NA</td>
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<td>-</td>
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<tr>
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features of these disorders. Poser and Brinar classified BCS and NMO into one group based on purely clinical considerations of chronicity and severity (5). Although it was pointed out in the review of BCS conducted by Kuroiwa in 1985 that BCLs occasionally coexist with Devic’s syndrome (6), these cases (16-18) were reported long before the discovery of NMO-IgG and the establishment of the current concept of NMO (1, 2, 7, 8).

Recently, a single case of comparatively and longitudinally extensive spinal cord lesions in a patient with BCS (20) and a single case of NMO with a BCL in the brainstem were reported (9). The clinical and laboratory characteristics of these cases are summarized in Table. Almost all of the patients presented with bilateral optic neuritis. The spinal cord lesions extended from two vertebral segments to more than three vertebral segments. NMO-IgG and anti-APQ4 antibodies were negative in the case reported by Marti et al. (21).

The extensive loss of APQ4 in the BCLs of four BCS patients was recently reported in a pathological study (10). The loss occurred in both demyelinated and myelinated layers of the BCLs, and the authors concluded that APQ4 loss can occur in patients with NMO and BCS. Furthermore, the same group showed that none of the Baló’s disease patients were positive for anti-APQ4 antibodies (11). Although a current dominant hypothesis of the origins of concentric demyelination in BCS patients involves distal oligodendroglialopathy mediated by hypoxia-like tissue injury and tissue preconditioning (22), it was recently proposed that antibody-independent astrocitopathy with APQ4 may cause tissue destruction via prolongation of vasogenic edema and amelioration of tissue damage due to reduced cytotoxic edema, thereby resulting in alternating bands of demyelination and preserved myelin (10, 11, 23). Our BCS case, which was characterized by negative test results for anti-APQ4 antibodies, may be in line with the antibody-independent hypothesis.

In conclusion, our case suggests that an immune mechanism other than anti-APQ4 antibodies may cause NMOsd with BCS. If loss of APQ4 is a common pathologic feature in the brains of patients with BCS, pathogenetic factors other than anti-APQ4 antibodies may cause BCL formation with a loss of APQ4. This case report may help to further understanding of the associations and pathogenesis of these disorders.

The authors state that they have no Conflict of Interest (COI).

Authors’ contributions
HM drafted the first manuscript and made a contribution to acquiring the data. MM revised the manuscript, leading to the final approval of the current submission. KK and YK revised the draft. SK revised the manuscript, leading to the final approval of the current submission. All authors read and approved the final manuscript.

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