Letter to the Editor

Persistent microscopic active inflammatory lesions in the central nervous system of a patient with neuromyelitis optica treated with oral prednisolone for more than 40 years

A R T I C L E  I N F O

Keywords:
Neuromyelitis optica
Long-term clinical course
Microscopic active inflammatory lesion
Oral corticosteroid therapy

A B S T R A C T

We have reported an autopsy case of neuromyelitis optica (NMO) that exhibited persisting active inflammatory lesions in the central nervous system (CNS) despite a 45-year-long treatment with oral corticosteroids. To our knowledge, our case had received the longest course of maintenance treatment. This case study suggests that the current treatment of NMO with immunosuppressive agents may offer a good prospect for improving life expectancy. On the other hand, it also suggests that microscopic active lesions which were clinically silent and difficult to detect by neurological examination or MRI studies may persist in the CNS in patients with NMO, despite prolonged and continuous immunosuppressive treatment.

Dear Editor,

Neuromyelitis Optica (NMO) is an inflammatory demyelinating disease of the central nervous system (CNS) that preferentially affects the optic nerve and spinal cord.

The diagnostic criteria for NMO have been revised and more effective therapeutic strategies have been developed since the aquaporin-4 (AQP4) disease-specific autoantibody was identified in 2004 [1]. Advances in the management of NMO are expected to improve the outcomes of patients with NMO. However, little is known about the long-term clinical course of the disease. We herein present an autopsy case of typical relapsing NMO that exhibited persistent active inflammatory lesions in the CNS after a long-term follow-up over 40 years.

1. Case reports

A 19-year-old woman presented with fulgurant back pain in 1966 (temporally referenced as year 0) and subsequently experienced two additional episodes during the same year. The following year, she developed paraparesis and numbness below the neck. She was treated with intravenous methylprednisolone and achieved partial recovery. At that time, she was diagnosed with relapsing/remitting multiple sclerosis, and maintenance therapy with oral prednisolone was started. The maximum dosage of prednisolone was 50 mg daily after each recurrence (Fig. 1A). At 41 years, a serum anti-AQP4 antibody test result was positive. At 43 years, she developed bladder cancer. Two years later, metastasis to the cervical vertebrae was found, and she died of respiratory failure 3 months later.

Autopsy was performed after obtaining informed consent from her family. Macroscopically, the spinal cord showed longitudinally transverse cystic necrosis extending from the cervical to the thoracic level. The optic tracts and chiasm were markedly atrophic. Neither old plaque formation nor marked atrophy was observed in the cerebellum or brain stem. On microscopic examination, the bilateral optic tracts showed marked loss of myelin and axons and an increased number of hyalinized vessels. From the cervical to thoracic cord, concentric microscopic active lesions were irregularly distributed in both the white and gray matter (Fig. 1B-D, G). Immunoreactivity for glial fibrillary acidic protein (GFAP) and AQP4 was totally defective in the old necrotic lesion (Fig. 1E, F). The lumbar and sacral cords were relatively preserved; however, acute inflammation with perivascular or parenchymal infiltration of abundant neutrophils and a few lymphocytes was observed in the gray and white matter (Fig. 1H, I). Numerous microglia/macrophages were infiltrated in the foci (Fig. 1J). In these active lesions, perivascular immunoreactivity for GFAP and AQP4 was defective (Fig. 1K). Similar microscopic active necrosis was found in the deep white matter of the right frontal lobe, left amygdala, and central pons.

2. Discussion

This patient was considered to have typical seropositive NMO with recurrent myelitis and optic neuritis. The clinical features of this case were worthy of attention because she survived for a long period of over 40 years after the onset of the disease. Several studies have addressed the clinical course of NMO. In one study conducted before the discovery of the 2006 Wingerchuk criteria for NMO [2], Thirty-three years after the onset of the disease, we increased the oral corticosteroids from 5 to 10 mg/day after an episode of recurrence. At 36 years, as maintenance therapy, we added methotrexate (5 mg/week) to the corticosteroid therapy because of disease recurrence and worsening diabetes. The patient experienced 45 clinical recurrences during a 38-year period. From 39 years onward, she did not develop clinically apparent recurrence (Fig. 1A). At 41 years, a serum anti-AQP4 antibody test result was positive. At 43 years, she developed bladder cancer. Two years later, metastasis to the cervical vertebrae was found, and she died of respiratory failure 3 months later.
A

Wheel chair bound  Bilateral severe visual impairment

Steroid diabetes

Bladder cancer

Death

Maximal dose after relapse: 50mg/day
Minimal dose in remission: 5mg/day

Oral corticosteroids

5mg/day  10mg/day  5mg/week

Methotrexate

B

C

D

E

F

G

H

I

J

K

(caption on next page)
of the AQP4 antibody, the 5-year survival rate of NMO was 68% [3]. Another study performed after the discovery of the AQP4 antibody reported that 9% of patients died after 75 months [4]. The prognosis of NMO has been considered to be poor. Although the functional prognosis does not appear favorable, early intervention with corticosteroids might improve the patient’s life expectancy [3,4], as shown in the present case.

It is also notably that the microscopic active lesions persisted in the lower lumbar cord and other areas of the CNS of our patient even during remission after a long-term clinical course. The characteristics of these lesions are compatible with those of previously described active NMO lesions [5,6]. In contrast with the improvement in mortality associated with early intervention, these findings suggest that the disease is persistent and resistant to immunosuppressive treatment, even 45 years after the onset of symptoms. Compared to current treatments for NMO, our treatment might have been insufficient to eliminate her disease activity [7]. However, these microscopic lesions were clinically silent and difficult to detect by neurological examination, laboratory tests, or MRI studies. Therefore, a clinical indicator that enables prediction of the disease activity during the period of clinical remission should be investigated in the future.

In summary, we have herein described an autopsy case of NMO who was treated with corticosteroids for more than 40 years, from the early stage of the disease, and survived for a long period. The current treatment of NMO with immunosuppressive agents including corticosteroids may be promising with respect to improving life expectancy [8]. In contrast, our case suggests that microscopic active lesions may persist in the CNS in patients with NMO during the remission phase despite a prolonged clinical course under continuous immunosuppressive treatment.

Conflict of the interest

None of the authors have conflict of interest associated with this manuscript.

Acknowledgments

We thank Dr. K. Tanaka (Niigata University Graduate School of Medicine, Niigata, Japan) for the AQP4-Ab assay.

References

[1] V.A. Lennon, D.M. Wingerchuk, T.J. Kryzer, et al., A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis, Lancet 364 (2004) 2106–2112.
[2] D.M. Wingerchuk, V.A. Lennon, S.J. Pittock, et al., Revised diagnostic criteria for neuromyelitis optica, Neurology 66 (10) (2006) 1485–1489.
[3] D.M. Wingerchuk, W.F. Hogancamp, P.C. O’Brien, et al., The clinical course of neuromyelitis optica (Devic’s syndrome), Neurology 53 (1999) 1107–1114.
[4] J. Kitley, M.I. Leite, I. Nakashima, et al., Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan, Brain 135 (2012) 1834–1849.
[5] C.F. Luechingetti, R.N. Mandler, D. McGavern, et al., A rule for humoral mechanisms in the pathogenesis of Devic’s neuromyelitis optica, Brain 125 (2002) 1450–1461.
[6] T. Misu, K. Fujihara, A. Kakita, et al., Loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis, Brain 130 (2007) 1224–1234.
[7] M.C. Papadopoulos, J.L. Bennett, A.S. Verkman, Treatment of neuromyelitis optica: state-of-the-art and emerging therapies, Nat Rev Neurol 10 (9) (2014) 493–506.
[8] S. Watanabe, T. Misu, I. Miyazawa, et al., Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis, Mult Scler 13 (2007) 968–974.

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