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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

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ABSTRACT

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 suggest 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 relapse, and the dosage was gradually tapered to 5 to 10 mg daily during remission. Eight years after the onset of symptoms, she developed optic neuritis in both eyes as well as severe myelitis that temporarily required mechanical ventilation. By 20 years after the onset of symptoms, she developed permanent visual disability, wheelchair dependence, and steroid diabetes. Magnetic resonance imaging (MRI) performed 30 years after the onset of the disease revealed a T2-hyperintense, longitudinally extensive lesion from C2 through C7. Brain MRI findings and immunological test results were normal. She also had a normal cell count, elevated total protein level (0.69 g/L), and negative oligoclonal bands in the cerebrospinal fluid. At that point, the patient's signs satisfied the 2006 Wingerchuk criteria for NMO [2]. Thirty-three years after the onset of symptoms, 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.

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 cerebrum 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, confluent or mostly transverse necrotic 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

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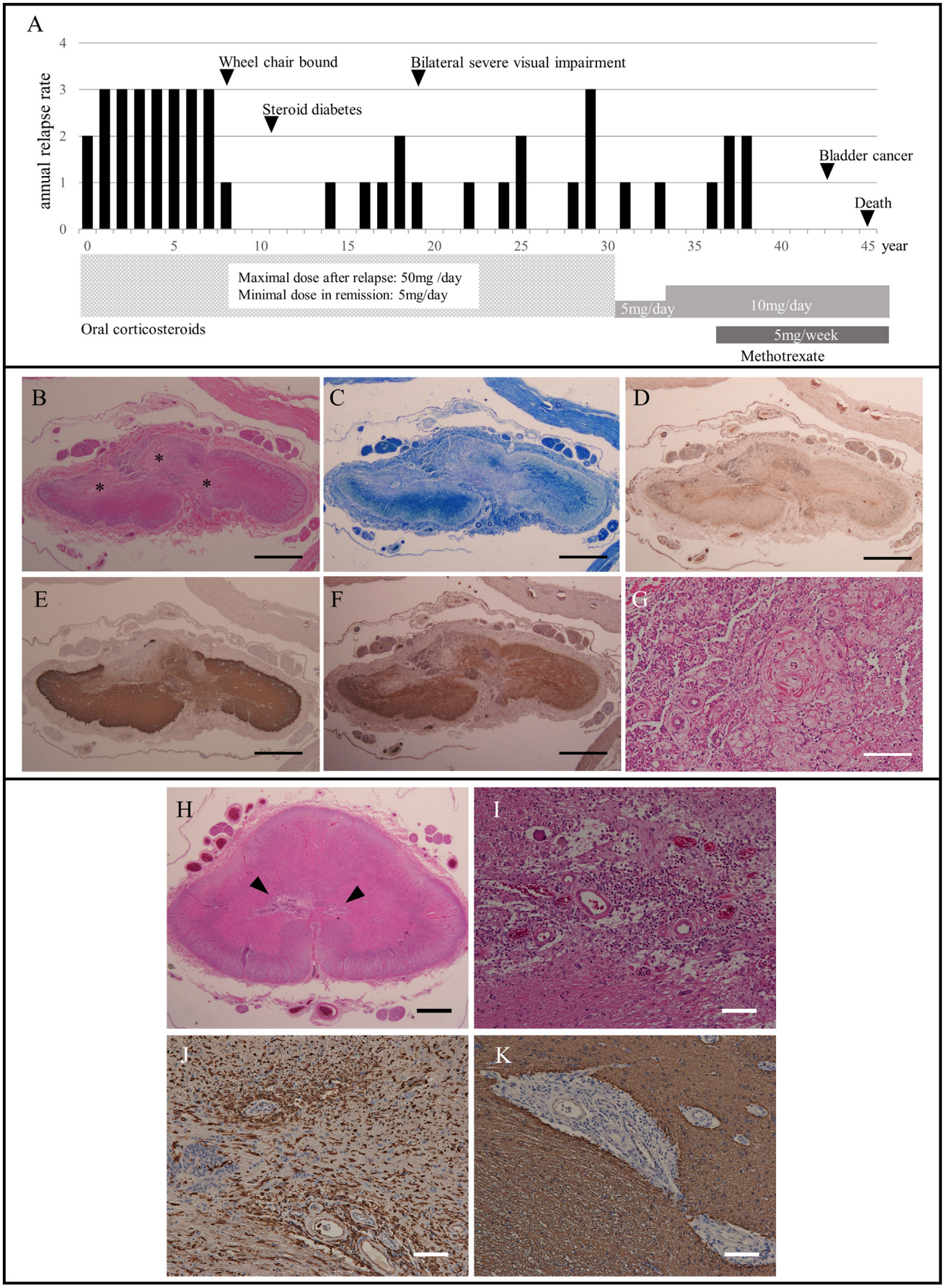

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Fig. 1. Clinical course and therapeutic interventions during remission (A). Pathological findings of a chronic lesion (B–G) and an early active lesion (H–K). Confluent necrotic lesions were observed in both the gray and white matter at the thoracic cord (Th4) (B, *). The lesions showed extensive demyelination (C) and severe loss of axons and neurons (D). Immunoreactivity for GFAP (E) and AQP4 (F) was totally defective in the old necrotic lesions. In the necrotic area, an apparent increase in blood vessels with thickened and hyalinized wall was observed (G). Microscopic active inflammatory lesions were observed around the central canal of the lumbar cord (H, arrowheads). Perivascular and parenchymal infiltration of numerous neutrophils, eosinophils, and lymphocytes was seen (I). Numerous microglia/macrophages that were immunoreactive for Iba1 were infiltrated in the foci (J). Perivascular immunoreactivity for GFAP was defective (K). B, G, H and I: HE stain; C: Klüver–Barrera stain. Immunohistochemistry for neurofilaments (D), GFAP (E and K), AQP4 (F) and Iba1 (J). Scale bars, 1000 μm (B, C, D, E, F and H), 130 μm (G) and 50 μm (I, J, and K).

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.

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