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An Autopsy Case of Elderly Onset Brainstem Acute Disseminated Encephalomyelitis

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Acute disseminated encephalomyelitis · Brainstem encephalitis · Inflammatory demyelination · Autopsy cases

Abstract
Acute disseminated encephalomyelitis (ADEM), which is a disease that causes multifocal inflammatory demyelination of the central nervous system, occurs predominantly in children and young adults. We report an autopsy case of an elderly man with brainstem ADEM that progressed over a period of about 3 months.
An 82-year-old man developed disturbance of consciousness, dysphagia, and ataxic gait over a period of about 3 months. He was admitted to another hospital for aspiration pneumonia and recovered but was transferred to our hospital due to prolonged disturbance of consciousness. The patient was able to follow simple commands but had a tendency to somnolence. In addition to meningeal stimulation signs, the patient had left-dominant upper and lower limb ataxia and right-dominant limb spasticity. Brain FLAIR/T2-weighted imaging showed high-intensity lesions from the brainstem to the middle cerebellar peduncle bilaterally, medulla oblongata and upper cervical spinal cord, and T1-weighted imaging revealed contrast-enhanced lesions in the left middle cerebellar peduncle and cervical spinal cord. Although spinal fluid examination revealed elevated proteins, other laboratory tests indicated no evidence of infection, vasculitis, collagen diseases or tumors, and anti-ganglioside, anti-AQP4 and anti-MOG antibodies were negative. After admission, the patient again developed aspiration pneumonia, which progressed to acute respiratory distress syndrome, and he died on the 15th day of hospitalization. Autopsy findings indicated acute and subacute demyelination mainly in the brainstem and cerebellum, and perivascular lymphocyte and macrophage infiltration in the areas of demyelination. A

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postmortem diagnosis of ADEM was made based on the generally monophasic course of the disease and the absence of regenerating myelinated sheaths.
There are very few reports of elderly patients with brainstem ADEM. ADEM should be considered as a differential diagnosis in patients with brainstem encephalitis.

Introduction

Acute disseminated encephalomyelitis (ADEM), which causes multifocal inflammatory demyelination of the central nervous system, mainly in the cerebral white matter, is predominantly a disease of children and young adults [1]. ADEM usually has a monophasic course, and most cases resolve with appropriate treatment. The brainstem might also be involved in this condition, although cases resembling brainstem encephalitis are rare.

The differential diagnoses of brainstem encephalitis vary widely, including infections, tumors, and autoimmune disorders. Recently, there have been reports of brainstem encephalitis associated with anti-myelin-oligodendrocyte glycoprotein antibody-related diseases [2], but the diagnosis is often difficult and it is not uncommon for the etiology to be unknown [3].

The pathological features of ADEM are perivenous demyelination, inflammatory cell infiltration of lymphocytes and macrophages around small veins, and demyelinating plaques [4]. It is also characterized by the absence of temporal differences in multiple foci. Distinct from the demyelinating plaques in multiple sclerosis, which was replaced by regenerated myelin sheath, the lesions in monophasic ADEM are replaced by nonspecific gliosis, which is its distinguishing feature.

In this article, we report an autopsy case of an elderly man with ADEM resembling brainstem encephalitis, which was clinically difficult to distinguish from other diseases. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529180).

Case Report

An 82-year-old man with no particular medical history had mild ataxic gait for several weeks. Subsequently, there was gradual progression of the gait disturbance, decreased daytime alertness, and he often choked during meals. Two months later, he was unable to walk by himself and eat without assistance. Two weeks later, he developed aspiration pneumonia and was admitted to another hospital. Although the pneumonia was well treated with antibiotics with adequate recovery, the disturbance of consciousness persisted, and hence, he was transferred to our hospital. At the time of transfer, he could open his eyes when called and follow simple commands, but he was otherwise in a somnolent state. There were no visual acuity or visual field disturbances, pupil diameter was 3 mm bilaterally, and light reflexes were rapid. Eye movements showed bilateral mild abduction disturbance, and facial muscles showed mild weakness bilaterally. Soft palate elevation and tongue protrusion were poor, and hoarseness and dysphagia were present. There was no limb muscle weakness. Pathological reflexes (Wartenberg, Troemner, Hoffmann, Babinski, and Chaddock) were negative, but there was mild clonus in the right upper and lower limbs. Bilateral limb cerebellar ataxia with left

predominance was noted. Nuchal rigidity and Kernig's sign were positive. It was difficult to assess superficial and deep sensations, sitting, standing, and walking.

Blood tests showed no abnormalities in blood cells, liver function, or renal function. Cerebrospinal fluid (CSF) examination showed protein-cell dissociation with a cell count of 1.0/μL (mononuclear cell count 1.0/μL) and protein level of 126 mg/dL. Evaluations for infectious diseases, collagen diseases, vasculitis, sarcoidosis, autoimmune diseases such as Behçet's disease, neoplastic diseases, and paraneoplastic syndromes ruled out these conditions in the differential diagnoses due to the absence of significant findings related to these conditions (Table 1). Anti-aquaporin 4 antibodies, anti-myelin-oligodendrocyte glycoprotein antibody, and anti-ganglioside antibody were also negative. Head magnetic resonance imaging (MRI) with diffuse FLAIR/T2-weighted imaging showed high-intensity areas from the pons to the midbrain, medulla oblongata, left-dominant middle cerebellar peduncle, right-dominant posterior limb of the internal capsule, and right-dominant upper cervical spinal cord (Fig. 1c–h); post-contrast T1-weighted imaging showed faint enhancement in the left middle cerebellar peduncle, cerebellum, and upper cervical spinal cord (Fig. 1i–l). Brain FLAIR/T2-weighted imaging presented high-intensity areas in the periventricular area, although there was no contrast effect. Other cerebral white matter lesions were not clear. MRI performed at the previous hospital 1 month after the onset of gait disturbance showed subdural hematoma that was almost completely absorbed, but FLAIR/T2-weighted imaging showed high-intensity lesions in the left middle cerebellar peduncle (Fig. 1a, b).

The patient had developed progressive loss of consciousness, cranial nerve palsies, dysphagia, cerebellar ataxia, and pyramidal tract disorders over the course of about 3 months. Based on the above findings and his clinical course, we suspected brainstem encephalitis. On the day of admission, the patient vomited and developed aspiration pneumonia; therefore, antibiotic therapy was commenced. However, his condition progressed to acute respiratory distress syndrome in a few days, and the respiratory condition did not improve. Additionally, considering the possibility of an inflammatory disease as a cause of the brainstem lesion, we administered two courses of methylprednisolone pulse therapy (methylprednisolone 1 g, 3 days), although there was no clinical effect and no improvement on imaging. The respiratory condition worsened further, and the family did not wish to prolong life. On hospital day 15, he passed away. With the consent of the family, we performed a pathological autopsy.

Pathology findings: The brain weight was 1,420 g. Grossly, there was mild frontotemporal lobe atrophy and mild diffuse cerebral edema. Histological findings indicated a strong inflammatory response in the brainstem, especially in the white matter from the basilar part of the pons to the left cerebellum, with a high degree of perivascular lymphocyte and macrophage infiltration, and demyelinating plaques with mild acute to subacute gliosis. These findings were also seen in the basal ganglia, right posterior capsule, left thalamus, left cerebral peduncle, and medullary reticular formation (Fig. 2a–f). Similar lesions were also seen in the periventricular cerebral white matter and white matter just below the calcarine sulcus, although the lesions were smaller and had milder inflammation and more progressive gliosis (Fig. 3a–d). Although there were older lesions in the periventricular cerebral white matter, considering the perivascular distribution, the generally monophasic stage of the disease, and the fact that the demyelinating plaques did not show regenerated myelin sheaths and mainly indicated gliosis, the histological findings were characteristic of ADEM.

Discussion

ADEM causes multifocal lesions in the central nervous system, mainly in the cerebral white matter, that might also involve the brainstem; however, "brainstem ADEM" with a

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Table 1. Diagnostic workup

	Result
CSF analysis	
Cell count and biochemistry	1WBC (2mono), 126 mg/dL protein, 48 mg/dL glucose
IgG index, myelin basic protein, and oligoclonal IgG band	Negative
Interleukin-6 in CSF	5.7 pg/mL
Autoimmune inflammatory disorder	
Blood count and kidney and liver functions	Normal
CRP and Erythrocyte sedimentation rate	0.99 mg/dL, 71 mm/(1h)
Immunoglobulins and complements	Normal
Anti-aquaporin 4 and myelin oligodendrocyte antibodies	Negative
Angiotensin-converting enzyme in serum and CSF	Negative
HLA genetic test gynecologic examination	No compatible with Bechet disease
Infectious disease	
Serum gram stain,βD glucan, HIV, HBV, HSV, VZV, EBV, CMV, Mycoplasma, VDRL	Negative
CSF gram stain and polymerase for HSV, VZV, tuberculosis	Negative
Neoplastic and paraneoplastic disorders	
Tumor makers	Normal
Anti-neuronal antibodies (anti-Hu, Yo, Ri, Tr, Ma2, GAD65, amphiphysin, CRMP5)	Negative
Cytology in CSF	Class III
Systemic computed tomography	No tumors

WBC, white blood cell; CRP, C-reactive protein; HLA, human leukocyte antigen; HSV, herpes simplex virus; VZV, varicella zoster virus; EBV, l Epstein-Barr virus; CMV, cytomegalovirus; VDRL, venereal disease research laboratory; GAD65, glutamic acid decarboxylase 65; CRMP5, collapsin response mediator protein 5.

distribution mainly in the brainstem and cerebellum, as in this case, is rare. Differentiating brainstem encephalitis in adults is a difficult task, and the cause is often difficult to identify. The various etiologies of brainstem encephalitis include infectious diseases, such as herpes and coxsackieviruses, neoplastic diseases such as lymphoma and brainstem glioma, and autoimmune-mediated diseases such as Bechet's disease, systemic lupus erythematosus, sarcoidosis, Bickerstaff brainstem encephalitis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, and paraneoplastic syndrome [3]. In many cases, as in this case, clinical findings do not clearly show disease-specific findings, but brainstem ADEM should be considered in the differentiation of brainstem encephalitis, and immunotherapy should be considered. Although two biopsy cases have been reported previously [5, 6], this case is the first autopsy report of brainstem ADEM. Clinically, the patient was old for typical ADEM and exhibited a protracted course and poor prognosis. Pathologically, this case was characterized by the presence of an acute lesion with greatest severity in the brainstem, with less severe inflammation in the surrounding areas, as well as cerebral white matter lesions in slightly different phases of development.

As far as we could determine, there are only 3 cases of brainstem encephalitis pathologically diagnosed as ADEM, including our case [5, 6] (Table 2). The other 2 cases were solitary lesions mainly in the brainstem and cerebellum and were diagnosed as ADEM by

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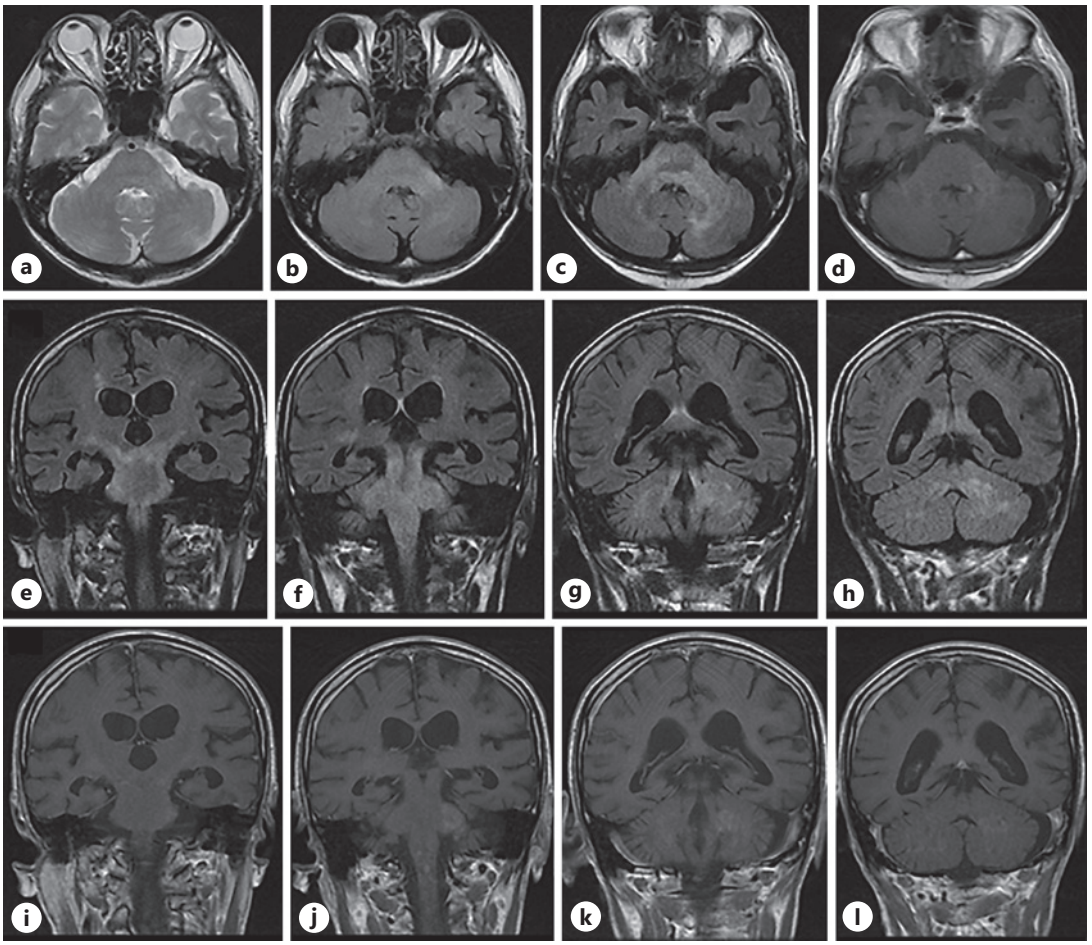

Fig. 1. Head MRI findings. Brain FLAIR/T2-weighted imaging performed at another hospital within 1 month after symptom onset revealed high-intensity lesions in the left middle cerebellar peduncle (**a**, **b**). Brain axial FLAIR/T2-weighted imaging at the time of the patient's first visit to our hospital showed high-intensity lesions from the left middle cerebellar peduncle to the entire brainstem (**c**), and post-contrast T1-weighted imaging demonstrated contrast enhancement in the left middle cerebellar peduncle (**d**). In addition, coronal FLAIR/T2-weighted imaging showed diffuse high-intensity lesions from the pons to the midbrain, medulla oblongata, left-dominant middle cerebellar peduncle, right-dominant, posterior limb of the internal capsule, and upper cervical spinal cord (**e–h**), and post-contrast T1-weighted imaging showed faint enhancement effects in the left middle cerebellar peduncle and upper cervical spinal cord (**i–l**).

biopsy. ADEM reportedly has an acute onset, with peak symptom severity occurring within a few days, followed by improvement within a few months. However, it took from several weeks to several months for symptoms to develop in all 3 cases, and residual symptoms and lesions were observed even after immunotherapy. Our case was older than the other 2 cases, had a longer course, and a wider range of lesions. In addition, there is a report of a pediatric case with a clinical diagnosis of brainstem ADEM that experienced rapid onset, rapid improvement, and no sequelae [7]. Adult cases tend to be more severe than pediatric ADEM cases [8], suggesting that the slow course and poor prognosis might be age-related. Studies on experimental autoimmune encephalomyelitis have shown that demyelinating diseases tend to be more severe and have a slower onset in older male mice [9]. It has been suggested that decreased function of CD4+ T cells and decreased activity of regulatory T cells might be

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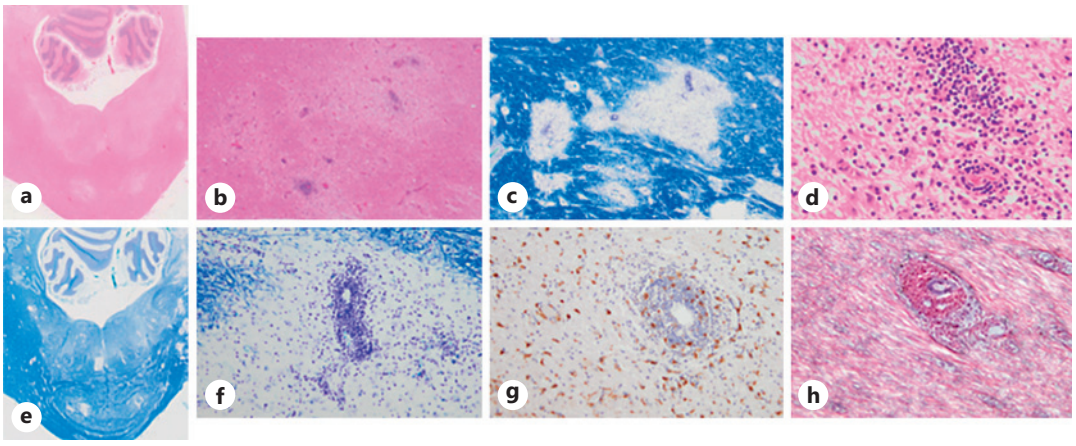

Fig. 2. Histological findings of the pons, middle cerebellar peduncle, and cerebellar white matter. There was severe perivascular lymphocyte and macrophage infiltration (**a**, **c**, **e**: hematoxylin-eosin staining, **g**: CD68 immunostaining). There was severe demyelination (**b**, **d**, **f**: Klüver-Barrera staining), although the axons were relatively well preserved (**h**: Bodian staining).

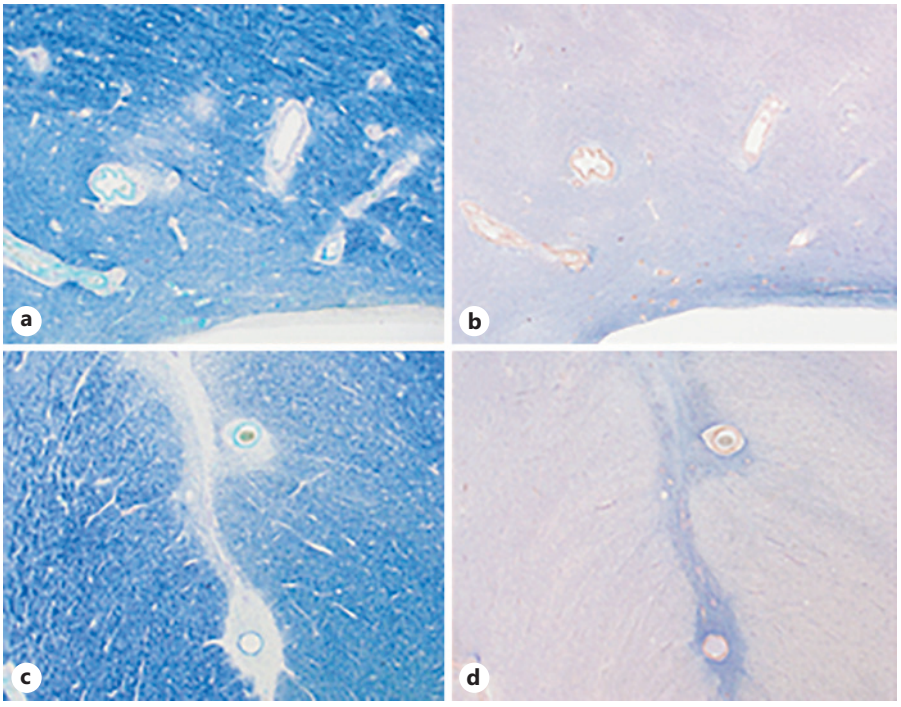

Fig. 3. Histological findings around the anterior horn of the lateral ventricle and of the white matter just below the calcarine sulcus. There were demyelinating lesions, but little inflammatory cell infiltration (**a**, **c**: Klüver-Barrera staining, **b**, **d**: Manlow's staining).

involved in the pathology of these diseases. In our case, although immunotherapeutic intervention might have been delayed, the patient was older than the previously reported cases and hence, might have been more severely affected.

In other 2 cases, the lesions were solitary lesions in the brainstem or cerebellum, but in our case, there were scattered lesions in the basal ganglia, thalamus, and posterior limbs of the

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Table 2. Previously reported cases of pathologically diagnosed ADEM

Case	Age/ sex	Symptom	Time to maximal defect	MRI	CSF	Biopsy/ autopsy	Treatment	Treatment response	Last EDSS	Clinicacl course
Present case	82/M	Drowsiness Dysphagia Gait disturbance	12 weeks	Brainstem (pons dominant) Middle cerebellar peduncle Cerebellum Posterior limb of internal capsule Corpus callosum Gd enhancement: middle cerebellar peduncle Cerebellum	WBC 1 Protein 126 OCB 0	Autopsy	IVMP	None	10	Fatal
Young et al. [5]	68/F	Diplopia Dysarthria Gait ataxia Face numbness	6 weeks	Pons Middle cerebellar peduncle Gd enhancement: pons Middle cerebellar peduncle	WBC 2 Protein 49 OCB 0	Biopsy	IVMP	Partial	7	Replacing stable at 1.5 years MRI lesion smaller, but leading edge of enhancement without lesions
Miler et al. [6]	36/F	Nystagmus Face numbness Gait ataxia Bulbar palsy	4 weeks	Tegmentum part of pons and medulla oblongata Gd enhancement: tegmentum part of pons and medulla oblongata	WBC 1 Protein 34 OCB 0	Biopsy	IVMP	Partial	8	After 18 months: severe disequilibrium, limb ataxia, bulbar weakness MRI: reduction in the size of the original lesion

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; WBC, white blood cell; OCB, oligoclonal bands; IVMP, intravenous methylprednisolone.

Table 3. Pathological inflammatory findings in this case

Lesions	Inflammatory	Phase
Cerebral cortex	–	
Cerebral white matter		
Periventricular, subcortical white matter	+	subacute-chronic
Corpus callosum	++	acute-subacute
Basal forebrain	++	acute-subacute
Basal ganglia	+	acute-subacute
Thalamus	++	acute-subacute
Posterior limb of internal capsule	++	acute-subacute
Mesencephalon		
Cerebral peduncle	++	acute-subacute
Pons		
Basilar, tegmentum part	+++	acute-subacute
Middle cerebellar peduncle	+++	acute-subacute
Medulla oblongata		
Reticular formation	++	acute-subacute
Cerebellar white matter	+++	acute-subacute
Cervical cord		
Upper part	++	acute-subacute
Lower part	–	

internal capsule. In addition, the brainstem area, especially near the pons and middle cerebellar peduncle, showed the evidence of intense inflammation on pathological evaluation, and the inflammatory findings were milder in lesions at a distance from these lesions (Table 3). In the other 2 cases, MRI images showed strong contrast-enhanced lesions in the pons and middle cerebellar peduncle. Pontine lesions have been reported to be the most common brainstem lesions in ADEM [10], suggesting that the pons might be prone to autoimmune diseases. In an autopsy case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, it was reported that the findings of inflammation were weaker in lesions more distant from the pons [11]. In this case as well, the area of maximum inflammation was found in the region of the pons and its surrounding area, and the lesion that was found on MRI 2 months earlier could have been the starting point of inflammation in the lesion.

Another feature of our case was the presence of advanced gliosis in lesions in the supratentorial cerebral white matter. Although ADEM has a basically monophasic course, there are also cases of multiphasic disseminated encephalomyelitis (MDEM), which have a recurrent course [12]. MDEM is diagnosed when a new demyelinating event that meets the diagnostic criteria occurs more than 3 months after the first event that meets the criteria for ADEM. In our case, the clinical symptoms were continuous for 3 months, which did not meet the diagnostic criteria for MDEM. However, there was no contrast effect on MRI of the same area at the time of observation in our hospital and it was difficult to distinguish this lesion from an ischemic lesion on previous MRI. Moreover, since it was a subclinical lesion, it was difficult to determine the demyelinating event when the lesion appeared. Since the pathological findings showed inflammatory demyelination, we cannot deny the possibility that the lesion was a prior lesion that developed before the current episode, and pathologically showed MDEM-like progress.

Pathological findings of MDEM have been reported in biopsy cases, with biopsy findings showing perivascular infiltration of mononuclear cells, demyelination, loose white matter, and foamy macrophages compatible with ADEM [13]. However, in the previous report, the biopsy was performed from an acute lesion and did not allow for evaluation of old lesions. In addition, Young et al. [5] reported 3 cases in which the pathology showed both perivenous demyelination of ADEM and confluent demyelination, a feature of multiple sclerosis, and 2 of the 3 cases had a relapsing course. However, confluent demyelination was not observed in the present case.

The lesion in the supratentorial cerebral white matter also had minor inflammatory demyelinating findings compared to the other lesions. The possible mechanism for the preceding cerebral white matter lesions that remained minor and subclinical, and the subsequent development and disproportionately severe progression of the brainstem lesions could be associated with the age-related immunological decline described above. In the other 2 cases, since the biopsies were obtained from the brainstem region and pathological findings in other regions were not examined, it is possible that subclinical lesions existed in the cerebral white matter in these patients. Since our case was an autopsy case, we were able to evaluate such subclinical and minor lesions as well. Our experience with the present patient suggests that the search for cerebral white matter lesions in cases of brainstem encephalitis may be challenging if the lesions are old, but the presence of lesions with a contrast effect might suggest the possibility of brainstem ADEM.

Our case suggests that brainstem ADEM is one of the clinical phenotypes of ADEM, in which the lesion is centered in the brainstem. In older patients, ADEM might progress in a different manner compared with young patients. Although brainstem encephalitis is often difficult to differentiate from ADEM, brainstem ADEM should be considered in the differential diagnosis, and early immunotherapeutic intervention should be considered in patients suspected to have this condition.

We experienced a case of ADEM that developed as brainstem encephalitis. Although brainstem encephalitis is often difficult to differentiate, brainstem ADEM should be considered in the differential diagnosis and early immunotherapeutic intervention should be considered.

Acknowledgments

The authors would like to thank the patient for his collaboration.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with the local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Yasuyuki Takai: conceptualized the study and collected the data. Shinsuke Tobisawa: evaluated the results and drafted the manuscript. Asuka Funai and Takashi Komori: collected and reviewed the pathological data. Kazushi Takahashi: participated in the design of the study and critically reviewed the results and manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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