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Neuropathologic Studies of Acute Multiple Sclerosis Mimicking Acute Encephalitis

Teruo SHIRABE, Izumi KAJIKAWA, Yasuto HIGASHI, Takashi FUKUYA and Yukio OHKITA*

Department of Human Pathology (Neuropathology),
**Department of Emergency Medicine,*
Kawasaki Medical School, Kurashiki 701-01, Japan

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ABSTRACT. Neuropathologic findings of acute multiple sclerosis mimicking acute encephalitis were described.

The patient was a 42-year-old man with acute febrile encephalitic symptoms and signs such as high fever, unconsciousness and convulsive seizures, and a monophasic course of 18 days duration. Pathologically, numerous inflammatory demyelinating lesions were scattered mainly in the cerebral and cerebellar white matter, the internal capsules, the putamen, the brainstem and the optic nerves. In particular, the demyelinating lesions of the brainstem were extensive and confluent, whereas those in the right occipital lobe were small and perivenous, reminiscent of acute disseminated encephalomyelitis. Axons in these demyelinating lesions were well preserved, with a considerable number of macrophages and partial proliferation of protoplasmic astrocytes.

There were no demyelinating lesions of concentric sclerosis type, which may occur in cases with acute multiple sclerosis. Pathological features in this case were typical of acute multiple sclerosis despite the symptoms and signs mimicking acute encephalitis and a clinical course of only 18 days duration.

Key words : acute multiple sclerosis — acute disseminated encephalomyelitis — neuropathology

Multiple sclerosis is a disease entity of unknown etiology in which demyelinating lesions with fibrillary gliosis are scattered throughout the central nervous system.[1—3] It involves mainly young adults between 15 to 50 years old. Clinically, it shows variegated symptoms and signs attributable to multiple demyelinating lesions in the central nervous system, and it is progressively aggravated with repeated remissions and exacerbations.[4] Unconsciousness and convulsive seizures are extremely rare in this condition. Its clinical course extends over several years or more in cases of the chronic relapsing Charcot type, or over several months in cases of the acute Marburg type.[2, 5]

We experienced an autopsy case of acute multiple sclerosis mimicking acute encephalitis with symptoms and signs such as high fever, unconsciousness and convulsive seizures, and a monophasic course of only 18 days duration. The purpose of this paper is to describe the clinical and pathological characteristics of this unusual case.

調 輝男, 梶川 泉, 東 靖人, 福屋 崇, 大北幸生

CASE REPORT

Clinical Course

A 42-year-old man was admitted to the Kawasaki Medical School Hospital because of fever and confusion on September 5, 1985.

He was well until eight days earlier when he noticed a fever of 39°C with vomiting. Two days later, he complained of urinary retention. On the day of admission, he became confused and was incoherent. The movements of the extremities became clumsy.

His past history and family history were non-contributory.

On physical examination, he was found to be confused and restless. His temperature was 37°C, his pulse was 100 and his blood pressure was 130/64 mmHg. The chest and abdomen were unremarkable.

Neurological examination revealed mild neck stiffness and Kernig's sign. He was awkward in movements of the extremities and occasional myoclonic seizures were seen in the upper extremities. There was no apparent weakness of the extremities. He had difficulty in urination.

The white blood cell count was 5,600 with a normal differentiation. A lumbar puncture yielded xanthochromic cerebrospinal fluid under a pressure of 300 H_2O. The fluid contained 348/3 white cells, of which 4% were neutrophils and 96% were lymphocytes. Protein was 300 mg/dl, and glucose was 48 mg/dl. An electroencephalogram showed a background activity of 8 to 9 Hz alpha waves with sporadic 4 to 6 Hz theta bursts predominantly in the occipital lobes and occasional 25 to 30 beta waves. Periodically, high amplitude sharp waves reminiscent of periodic lateralized epileptiform discharges were observed in the left central and temporal areas and in the right central area. A computed tomographic scan of the brain disclosed extensive low densities in the white matter of the bilateral fronto-parietal lobes, the midbrain and pons. A brainstem auditory evoked response did not elicit any other peaks following the first peak, which suggested severe brainstem dysfunction. The titer of the serum for herpes simplex virus type 1 was elevated 40 times. Titers for other viruses were all within normal range,

On the night of the admission, he developed status epilepticus and became comatose. He was diagnosed as herpes simplex encephalitis and treated with barbiturates, adenine arabinoside and globulin product. The convulsions were controlled, but his consciousness remained comatose thereafter. On the 6th hospital day, an electroencephalogram revealed a diffuse and slow activity of low voltage. Light reactions were not seen. Three days later, he developed bronchopneumonia. He died on September 15, 1985, 18 days after the onset of his illness. Corticosteroids were not administered during the course of the illness.

Pathological Findings

A general autopsy revealed bronchopneumonia, pulmonary edema, acute pancreatitis and an infectious spleen.

The brain weighed 1,500 g. Leptomeninges over the convexity of the cerebral hemispheres were turbid. Serial coronal sections of the brain were edematous and congestive. Confluent softened lesions, translucent and yellow-brown in color, were scattered in the white matter of the cerebral and cerebellar hemispheres, and in the brainstem, with occasional petechial hemorrhages.

Histologically, there were infiltrations of lymphocytes, monocytes, plasma cells and macrophages, and focal hemorrhages in the subarachnoid space. Myelin stains of the cerebral hemispheres showed numerous sharply demarcated, completely or occasionally incompletely demyelinating lesions of various shapes and sizes up to 1.5 cm, mainly in the deep white matter, around the lateral ventricles, in the internal capsules, right globus pallidus, left putamen and corpus callosum (Fig. 1). Demyelinating lesions of the deep white matter were overlaid by a widespread vaguely demarcated pallor lesion. In addition, small perivenous demyelinating lesions, up to 1 to 2 mm in diameter, were scattered in the white matter of the right occipital lobe (Fig. 7).

These demyelinating lesions were intensely cellular with prominent perivascular infiltrations of lymphocytes, monocytes and plasma cells, and considerable numbers of diffusely scattered macrophages and some proliferation of protoplasmic astrocytes (Figs. 4, 9). These macrophages had no tendency to accumulate perivascularly. Occasional hemorrhages were found, especially in the brainstem. Neutrophils and fibrins were observed in the vessel walls and perivascular spaces of the white matter of the left fronto-parietal lobe (Fig. 8).

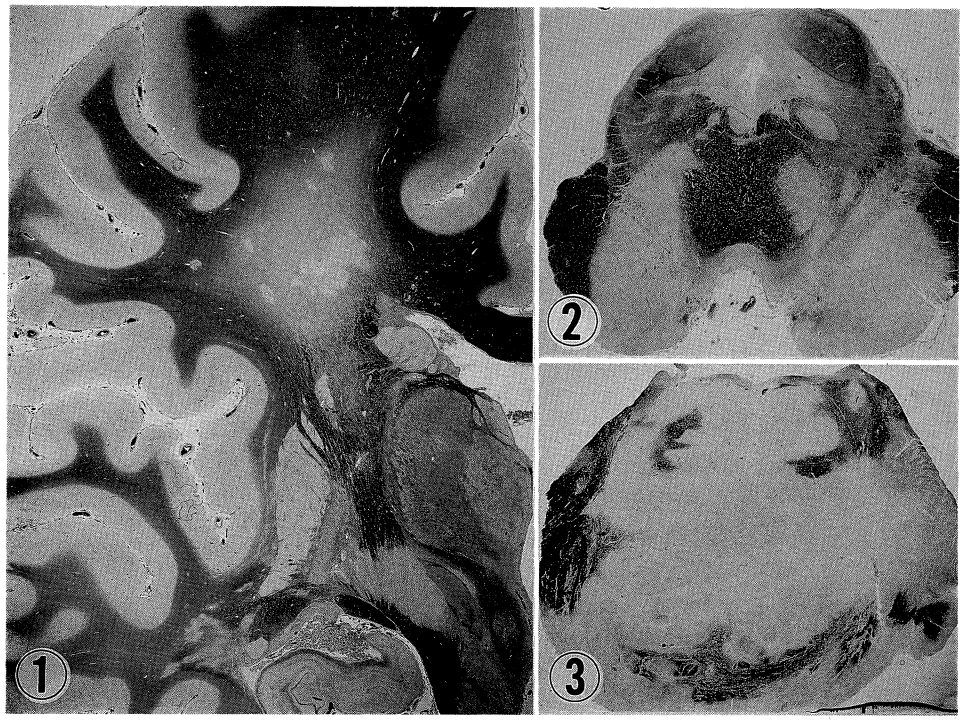

Fig. 1. Coronal section of the right cerebral hemisphere just caudal to the mammillary body stained for myelin. Numerous demyelinating lesions are seen in the deep white matter, around the lateral ventricle, internal capsule and globus pallidus. Demyelinating lesions of the deep white matter are overlaid by a widespread, vaguely demarcated pallor lesion. Klüver-Barrera, ×1.3

Fig. 2. Section of the midbrain showing sharply demarcated demyelinating lesions in the tegmentum, substantia nigra, cerebral peduncles and around the cerebral aqueduct. Klüver-Barrera, ×2.3

Fig. 3. Lower pons with extensive and confluent demyelinating lesions in the tegmentum and base. Klüver-Barrera, ×2.0

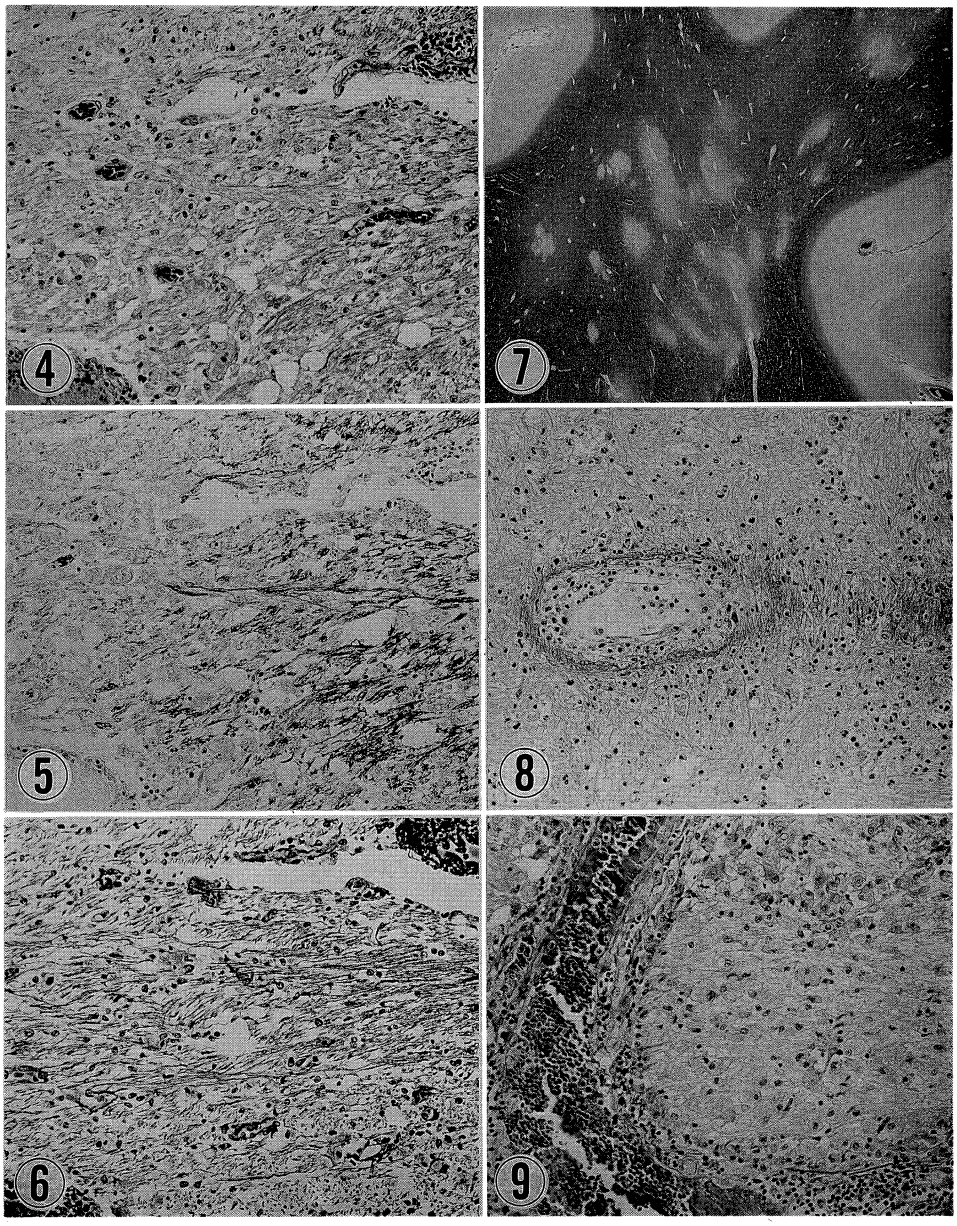

Fig. 4. Photomicrograph of the border zone of a demyelinating lesion of the midbrain. There are perivascular lymphocytic infiltrations, diffusely scattered macrophages and proliferation of astrocytes. H & E, ×134

Fig. 5. Border zone of the same demyelinating lesion as in Fig. 4. Left half of the photograph is demyelinated. Klüver-Barrera, ×134

Fig. 6. Border zone of the same demyelinating lesion as in Figs. 4 and 5. Axons are spared in the demyelinated lesion on the left side. Bodian, ×134

Fig. 7. Low power microscopic view of the white matter of the right occipital lobe scattered with small perivenous demyelinating lesions. Klüver-Barrera, ×2.1

Fig. 8. Neutrophils and fibrins are seen in the vessel wall and perivascular space of the white matter of the left fronto-parietal lobe. H & E, ×134

Fig. 9. Photomicrograph of a demyelinating lesion of the pons showing perivascular infiltrations of lymphocytes, monocytes and plasma cells, diffusely scattered macrophages and proliferation of protoplasmic astrocytes. H & E, ×134

Axons in these lesions were generally well preserved with Bodian's silver staining, with only occasional axonal swellings (Fig. 6). Fibrillary gliosis was not seen.

Small demyelinating lesions were scattered also in the cerebellar cortex and white matter. Extensive, confluent and sharply demarcated demyelinating lesions were observed in the tegmentum, substantia nigra, cerebral peduncles and around the cerebral aqueduct of the midbrain (Figs. 2, 5), around the floor of the fourth ventricle, the tegmentum and base of the pons (Fig. 3), and in the bilateral pyramidal tracts and left inferior olivary nucleus of the medulla oblongata. Patchy demyelinating lesions were frequently observed in the regions adjacent to the subarachnoid space in these areas. Some nerve cells of the substantia nigra, pontine nuclei, inferior olivary nuclei, cerebellar granular layer and dentate nuclei in the demyelinating lesions were somewhat chromatolytic or necrotic, but the majority of the nerve cells in the lesions were well preserved.

Optic nerves, especially in their intraorbital parts, showed extensive demyelination with mild fibrillary gliosis.

The spinal cord was not available for pathological examination.

DISCUSSION

The patient had acute febrile encephalitic symptoms and signs such as high fever, unconsciousness and convulsive seizures, and a progressive monophasic course of only 18 days duration. The titer of the serum for herpes simplex virus type 1 was elevated as much as 40 times. An electroencephalogram showed high amplitude sharp waves resembling periodic lateralized epileptiform discharges, which are characteristically observed with herpes simplex encephalitis.[6] Based on these clinical features, he was tentatively diagnosed as a case of herpes simplex encephalitis and treated as such with no effect. Multiple sclerosis was not taken into consideration before his death.

The main neuropathological findings were as follows: 1. The brain was edematous. 2. Numerous demyelinating lesions were scattered throughout the central nervous system. In particular, extensive, confluent and sharply demarcated demyelinating lesions were observed in the brainstem. 3. Demyelinating lesions of the deep white matter of the cerebral hemispheres were rather vaguely demarcated. 4. Small perivenous demyelinating lesions were scattered in the white matter of the right occipital lobe. 5. Inflammatory cellular infiltrates were prominent both in the subarachnoid space and in the perivascular spaces of the cerebral parenchyma. 6. Neutrophils and fibrins were observed in the perivascular spaces in the white matter of the left fronto-parietal lobes. 7. Petechial homorrhages were found in various places. 8. Axons were generally well preserved even in the extensively demyelinating lesions. 9. The majority of the nerve cells in the lesions were well preserved in general, even though

some nerve cells had been chromatolytic or necrotic. 10. Considerable number of macrophages were scattered in the demyelinating lesions. They had no tendency to accumulate perivascularly. 11. There was some proliferation of protoplasmic astrocytes in these lesions. Fibrillary gliosis was seen only in the optic nerves.

These pathological findings showing extensive demyelinating lesions are compatible with those of acute multiple sclerosis, except for the right occipital lobe, where small perivenous demyelinating lesions reminiscent of acute disseminated encephalomyelitis[3] were observed. This right occipital lobe lesion may suggest the close relationship with acute disseminated encephalomyelitis in our case. Other pathological findings, however, are typical of acute multiple sclerosis. Marked cellular infiltrates may be explained both by the fulminant course of the disease itself and by the fact that anti-inflammatory drug such as corticosteroids were not administered before the patient's death. Relative scantiness of astrocytic reaction except the optic nerves may also be explained by the short duration of the illness. Vaguely demarcated demyelinating lesions in the white matter of the cerebral hemispheres and some chromatolytic or necrotic nerve cells may be explained by cerebral edema due to increased vascular permeability in the process of the formation of the demyelinating lesions, and by the overlay of an anoxic-metabolic injury due to cardio-pulmonary dysfunction during deep coma.

Unconsciousness from the early days of the illness may have been due to diffuse cerebral edema plus extensive demyelinating lesions of the brainstem. Such cases as these with acute encephalitic symptoms and signs, and short monophasic course are rare in the literature.

It is said that acute multiple sclerosis occurs most commonly in relatively young patients, often preceded by a feverish illness and characterized by rapid deterioration and death within a few months.[2] The difference between acute multiple sclerosis and chronic relapsing multiple sclerosis may be quantitative.

Not a few cases of multiple sclerosis in Japan[7] have been reported to develop with an acute onset, occasionally accompanied by fever, but predominant symptoms and signs are those of the optic nerves and spinal cord involvement, unlike our case.

Harper[8] described a case of acute multiple sclerosis mimicking stroke with a course of 18 days. The patient was a 48-year-old woman who developed a stroke-like episode with dysphasia, urinary incontinence, right hemiplegia, and, at a later stage, coma, high fever and decerebrated rigidity. Pathological examination revealed diffuse concentric demyelinating lesions in the white matter of the bilateral cerebral hemispheres. These findings were those of acute multiple sclerosis of the concentric sclerosis type, first described by Baló[9] in 1928. This type of multiple sclerosis is also said to occur in younger individuals, and the onset is usually acute. Symptoms may be suggestive of space-occupying lesions and headache is a prominent symptom. The third case of acute multiple sclerosis described by Marburg[10] in 1909 had also showed concentric demyelinating lesions. Clinically, our case seems to be similar to this type of multiple sclerosis, but, pathologically, demyelinating lesions suggestive of concentric sclerosis were not found in our case.

Pogacar and Mendes[11] reported a 25-year-old man with acute multiple sclerosis who had a rapidly progressive course of 29 days duration. Pathological

examination demonstrated numerous demyelinating lesions mainly in the cerebral white matter and brainstem. The histological findings of their case are similar to ours, but ours was of shorter clinical course and probably therefore there were less severe macrophagic and astrocytic reactions. Banerjee and his co-workers[12] reported a similar case of acute multiple sclerosis. The patient developed high fever, headache and consciousness disturbance, who was diagnosed as acute disseminated encephalomyelitis and died 4 weeks later. Postmortem examination showed extensive demyelination of the cerebral white matter and smaller patches in the pons and cerebellum. This case also seems to have shown more pronounced astrocytic gliosis than ours in accordance with a longer course than ours. Otherwise, however, the clinico-pathological findings were quite similar to ours.

The pathogenesis of multiple sclerosis is unknown despite many years of study. Two major hypotheses have been advocated; that of a persistent slow viral infection on the one hand, and of an alteration of the immune system on the other.[13] As for the immune mechanism, both cell mediated immunity and humoral immunity have been proposed. Neutrophilic infiltrates and fibrinous deposits may show that some allergic mechanism played a part in the formation of the demyelinating lesions in our case. In particular, the diffuse edema in and around the demyelinating lesions suggests that humoral immunity is involved.

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