An Autopsy Case of the Marburg Variant of Multiple Sclerosis (Acute Multiple Sclerosis)

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Abstract

We herein report an autopsy case of the Marburg variant of multiple sclerosis (MS). A 29-year-old woman developed acute and progressive neurological symptoms. A diagnosis of MS was suspected based on the patient’s clinical background and brain MRI findings and the lack of evidence of malignancy on a brain biopsy. Despite the administration of typical treatment for MS, a fatal outcome occurred three months after disease onset. The autopsy revealed multiple inflammatory demyelinating lesions in the central nervous system. In addition, two noteworthy histopathological features were observed compared with prototypical MS. We evaluate the pathogenic differences between the Marburg type and prototypical MS by discussing the neuropathology and cerebrospinal fluid (CSF) findings of our case.

Key words: multiple sclerosis (MS), Marburg, inflammatory demyelinating disease (IDD)

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that exhibits heterogeneity in its clinical course, neuroradiological appearance and neuropathological features of its lesions. The Marburg variant of MS (1-16) is a rare, acute and monophasic variant of MS. By definition, it is a severe inflammatory demyelinating encephalomyelitis that leads to death within one year of disease onset. No consensus exists regarding the underlying pathogenesis of or beneficial treatments for MS, particularly with respect to the fulminate variant. On neuropathological grounds, the lesions of the Marburg type are more widespread than those of prototypical MS, with inflammatory demyelination occurring either diffusely or in multifocal lesions. In addition, the lesions are more destructive and are associated with severe axonal injury and necrosis with dense cellular infiltrates. The cellular infiltrates primarily consist of macrophages containing myelin breakdown products and enlarged astrocytes. In past neuropathological examinations, the lesions of the Marburg type have generally been found to be similar to those of prototypical early MS, although they tend to have more inflammatory infiltrates and appear more destructive. Therefore, the details of the pathogenic heterogeneity of the Marburg type and prototypical MS have not yet been clarified.

We herein report a rare autopsy case of the Marburg variant of MS and explore the underlying pathogenesis by comparing the findings with those of past reports of the Marburg type and prototypical MS.

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Case Report

Clinical summary

A 29-year-old woman was admitted to our hospital for a one-month history of decreased sensation, paresthesia and paralysis, starting in the left leg and spreading to the left arm. There was no history of preceding infection or vaccination. The patient was given a topical corticosteroid preparation for atopic dermatitis. She had no history of allergic diseases, such as asthma. There were no abnormalities in her vital signs or physical findings, except for the atopic dermatitis. There were no symptoms of meningeal irritation. A neurological examination revealed decreased sensation, paresthesia and paralysis in the left arm and leg.

On brain MRI, there were two ring-enhanced lesions in the right parietal periventricular white matter and a gadolinium-enhanced lesion in the right frontal periventricular white matter, with hyperintensity on T2-weighted images (WI) and hypointensity on T1WI. The neighboring cortical gray matter also exhibited hyperintensity on T2WI and hypointensity on T1WI (Fig. 1a-c). Whole-spine MRI revealed no spinal cord lesions.

Laboratory tests showed no abnormalities in the blood cell count, differential white blood cell count or biochemical parameters. The serum anti-aquaporin-4 (AQP4) antibody titer was negative. A cerebrospinal fluid (CSF) examination showed elevated levels of cells of 20/μL (mononuclear cell-dominant), protein of 71 mg/dL and myelin basic protein (MBP) of >2,000 pg/mL and an IgG index of 0.71 (normal, 0.28-0.66). There were no oligoclonal IgG bands in the CSF. The pretreatment CSF cytokine/chemokine levels demonstrated elevation of type II helper T-cell (Th2) cytokines/chemokines, such as eotaxin (4.73 pg/mL), IL-5 (22.2 pg/mL) and IL-10 (12.19 pg/mL), compared with the findings of past studies regarding CSF cytokine/chemokine profiles (17, 18). In contrast, the levels of INF-γ (<0.64 pg/mL), IL-2 (0.91 pg/mL), IL-9 (5.02 pg/mL) and IL-17 (0.45 pg/mL) were not increased (Fig. 2). The patient’s CSF cytokine/chemokine profile was measured using the MILLIPLEX® MAP HUMAN CYTOKINE/CHEMOKINE KIT. No malignant tumors were observed on whole-body CT or 18F-fluorodeoxy glucose positron emission tomography (FDG-PET) imaging. To rule out a primary brain tumor, the patient underwent a brain biopsy of the right parietal ring-enhanced lesion. The specimens obtained during the biopsy did not show any neoplastic tissue. Instead, destructive lesions with macrophage-dominant inflammatory infiltrates, edematous changes and proliferation of astrocytes in the cerebral parenchyma were observed, thus suggesting necrosis due to ischemia (Fig. 3a). Perivascular inflammatory infiltrates, including a mixture of lymphocytes, plasma cells, macrophages, eosinophils and a small number of neutrophils, were observed around the capillaries and venules (Fig. 3b). The infiltrating lymphocytes consisted of both B-cells (Fig. 3c, d) and T-cells (Fig. 3e). In addition, large lymphocytes positive for CD30 (Fig. 3f) and CD20 (Fig. 3g) were scattered around the vessels. Some of the infiltrates had invaded the vessels; however, no fibrinoid degeneration or thrombus formation were observed. A brain biopsy suggested the possibility of lymphomatoid granulomatosis (LYG) (19-21) as a differential diagnosis. Most systemic LYGs are EBV-associated B-cell proliferative disorders; hence, we were unwilling to make such a diagnosis in the absence of positivity for in situ hybridization of EBV-encoded mRNA (Fig. 3h). Following the biopsy, one month after disease onset, the patient was treated with oral steroids (betamethasone: 10 mg/day × 7 days) and weekly intravenous methylprednisolone (1 g/day × 3 days, three times). Nevertheless, she continued to worsen clinically and developed a visual field defect, weakness in all four extremities and a disturbance of consciousness. Serial brain MRI showed a reduction in the size of the two right parietal ring-enhanced lesions (Fig. 1d), while the diffuse Gd-enhanced and T2WI hyperintense periventricular lesions had progressed throughout the entire cerebrum (Fig. 1e). Furthermore, the last MRI performed three months after disease onset revealed new T2 hyperintense lesions in the medulla oblongata (Fig. 1f). The patient missed the chance to undergo another spinal MRI examination. A course of plasma exchange administered for a total of five days failed to halt the progression of the disease, and the patient died three months after symptom onset as a result of respiratory failure.

Pathological findings

An autopsy was performed five hours after the patient’s death. Her height was 163 cm, her body weight was 37.2 kg and her brain weight before fixation was 1,250 g. Macroscopically, multifocal lesions with tissue softening and coloration were noted throughout the central nervous system (Fig. 4a).

Whole mount brain and spinal cord sections showed multifocal, relatively well-bordered lesions, presenting as myelin pallor (Fig. 4b-f). In the cerebrum, the lesions were primarily localized to the periventricular white matter, including the ring-enhanced right parietal lesions that had been detected on MRI. In addition, some lesions affected the cortical gray matter (Fig. 4b, c, g). In the brain stem (Fig. 4d) and spinal cord (Fig. 4e, f), multifocal lesions were observed in the gray and white matter, as well as in the meninges (Fig. 4h).

Microscopically, perivascular inflammatory infiltration was a notable feature of the lesions in both the parenchyma and meninges. The infiltrates consisted of a mixture of lymphocytes, macrophages, plasma cells, eosinophils and neutrophils. In some of the lesions, the infiltrates had invaded the blood vessel walls; however, the lesions were neither destructive nor occlusive of the vessels. Both hyalinization and fibrosis of the vessels were absent (Fig. 4i, j). There was no deposition of IgG or complement around the vessels. Luxol fast blue stain (LFB) demonstrated the presence of multiple
perivascular myelin pallor lesions with inflammatory infiltrates. The lesions were observed not only in the white matter, but also in the gray matter. In the periventricular white matter, the myelin pallor lesions were fused and widespread. In the cortical gray matter, myelin pallor lesions were observed beneath the pia mater and in the neighboring cortices (Fig. 4c, g). The myelin pallor lesions with active perivascular inflammatory infiltrates demonstrated diminution of MBP immunoreactivity (Fig. 4k, l), and glial fibrillary acid protein (GFAP)-positive gemistocytic astrocytes were widely observed in the lesions (Fig. 4m). AQP4 immunostaining revealed patchy diminution of immunoreactivity (Fig. 4n). Creutzfeldt cells were occasionally noted in the background of marked gliosis in the demyelinating plaques (Fig. 4o). Macrophage infiltration was observed around the perivascular areas of the myelin pallor lesions. The lesions were found to be remarkably well defined following immunohistochemistry for macrophages (Fig. 5a). Axonal injury was noted in the lesions, thus correlating with the degree of inflammation and demyelination. The perivascular lesions with massive inflammatory infiltrates demonstrated fragmentation of axons and necrotic changes (Fig. 5b, c). In contrast, phosphorylated neurofilament (pNF)-positive axon cylinders and Nago-A-positive oligodendrocytes were relatively pre-

Figure 1. (a-c) Pretreatment and preoperative brain MRI. Gd-enhanced T1WI images showed two ring-enhanced lesions in the right parietal periventricular white matter with an additional right frontal periventricular white matter lesion. Sagittal (a) and axial (b) sections of Gd-enhanced T1-weighted images and an axial section of a T2-weighted image (c). (d-f) Post-treatment brain MRI. The two right parietal ring-enhanced lesions had decreased in size (d), while diffuse Gd-enhanced and T2 hyperintense periventricular lesions had progressed throughout the entire cerebrum (e). T2WI images revealed new lesions in the medulla oblongata (f, circle).
served compared with the distinct myelin destruction (Fig. 5d-g). This finding supports the notion that the lesions were not due to necrosis resulting from ischemia, but were instead caused by inflammatory demyelination.

An immunohistochemical analysis revealed the cellular components of the perivascular inflammatory infiltrates in the parenchyma and meninges. When the proportion of each lymphocyte type was calculated by counting immunocytochemically-positive cells around 10 vessels in a high-power field, CD20+ B-cells (69.0%) outnumbed CD3+ T-cells (25.0%), CD8+ cytotoxic T-cells (4.1%) and CD4+ helper T-cells (1.1%) (Fig. 5h-m).

In situ hybridization of Epstein-Barr virus (EBV)-encoded mRNA and latent membrane protein-1 (LMP-1) was negative (Fig. 5n, o).

To exclude the possibility of LYG lymphoma, we analyzed the frozen specimens obtained from the right parietal lesions (Fig. 4a, arrow) using Southern blotting. We did not observe any monoclonal rearrangement of the immunoglobulin heavy chain or T-cell receptor gene. A general autopsy revealed no LYG-related lesions in other organs, such as the lungs or kidneys.

The postmortem pathological findings revealed multifocal and disseminated inflammatory demyelinating lesions in the central nervous system (CNS). Inflammatory demyelinating diseases (IDDs) consist of a wide spectrum disorders, including prototypical MS, tumefactive MS, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO), Baló’s concentric sclerosis (BCS) and the Marburg variant of MS (1, 2). The clinical course and neuropathological findings of our case were consistent with a diagnosis of Marburg type MS: 1) the patient experienced a rapid and lethal clinical course, and her disease was refractory to typical therapies for MS; and 2) an autopsy revealed widespread inflammatory demyelinating lesions associated with severe axonal injury and necrosis with dense cellular infiltrates and giant reactive astrocytes. NMO also exhibits widespread inflammatory demyelinating lesions often accompanied by axonal alternations, such as swelling or spheroids and necrosis (16, 22). We excluded the possibility of NMO due to the absence of the unique pathological features of that disease. Our patient did not demonstrate deposition of immunoglobulin or complement, while NMO cases involve perivascular rosette and rim patterns of IgG deposition colocalized with complement activation. Hyalinization and fibrosis of the vessels are typically present in NMO cases; however, these features were absent in our case. MBP-stained myelinated fibers are relatively preserved in acute NMO lesions, whereas AQP4 and GFAP are lost. However, preserved GFAP, patchy loss of AQP4 and loss of MBP immunostaining were observed in our case. AQP4 loss can occur in heterogeneous demyelinating conditions, including NMO and MS (23, 24); however, the ‘patchy’ loss of AQP4 immunoreactivity observed in our case is one of the important neuropathological findings used to exclude the possibility of NMO, as originally described by Sharma R et al. (23). Marburg type MS is considered to be a particular variant of MS characterized by a severe and rapid clinical course and unusual neuropathological changes compared with prototypical MS. Only a few cases and studies (3-16) of Marburg type MS have been reported in detail. Previous studies have demonstrated the neuropathological changes of the Marburg type of MS. Clear differences are observed between the Marburg type and prototypic MS, including the fact that extension of the lesions is widespread and the degree of inflammatory demyelination is severe in patients with the Marburg type. With respect to extension of the le-
Figure 3. (a) A low-power field view of the biopsy specimen. Destructive changes with perivascular inflammatory infiltrates, edematous changes and proliferation of astrocytes were observed. Hematoxylin and Eosin staining, ×2.5 objective. (b) Perivascular inflammatory infiltrates. Mononuclear cells, plasma cells, eosinophils and a small number of neutrophils were observed. Hematoxylin and Eosin staining, ×40 objective. (c-g) The perivascular infiltrates consisted of both small B-cells (c: CD20, ×20 objective, d: CD79a, ×20 objective) and T-cells (e: CD3, ×20 objective). In addition, large lymphocytes positive for CD30 (f: ×40 objective) and CD20 (g: ×40 objective) were scattered around the vessels. (h) The in situ hybridization study of EBV-encoded mRNA was negative (×20 objective).

In addition to the neuropathological findings of our case, the white matter is a major target of the Marburg type. In contrast, only sparse cortical demyelination has been reported in the forebrain (13) and cerebellum (14) in patients with the Marburg type. The presence of inflammatory infiltrates in the meninges is not dominant compared with that observed in other types of MS (13). In regard to the components of the inflammatory infiltrates, prominent T-cell infiltrates are seen in active lesions. The number of B-cells is 10 times lower on average in comparison to that observed for T-cells (15). Eosinophils are observed in rare cases of the Marburg type (4% of cases; three of 73) (16). Compared with previous reports of the Marburg type and prototypical MS, our patient exhibited two noteworthy neuropathological features: 1) meningeal inflammation and gray matter lesions with inflammatory infiltrates were widespread and severe; and 2) perivascular inflammation was a prominent finding in the lesions, and the inflammatory infiltrates consisted of a mixture of various cells, being B-cell, not T-cell, dominant.

In addition to the neuropathological findings of our case,
Figure 4. (a) Macroscopic findings. A periventricular lesion with tissue softening and coloration was observed in the right parietal lobe (arrow). The specimens used for the histopathological analysis conducted at the biopsy and the assessment of immunoglobulin heavy chain and T-cell receptor gene rearrangement performed at autopsy were taken from this lesion. (b, c) Semimicroscopic view of whole mount cerebral sections. Multifocal lesions with myelin pallor were noted. The lesions were primarily localized in the periventricular white matter. In addition, cortical gray matter lesions were focally observed (b: Hematoxylin and Eosin staining, c: LFB, ×4 objective). (d-f) Brain stem and spinal cord sections (d: medulla oblongata, e: cervical cord, f: thoracic cord). Lesions were observed in both the gray and white matter. (g) Subpial and cortical lesions in the cerebrum. (LFB, ×4 objective). (h-j) Perivascular inflammatory infiltrates in the leptomeninges (h: Hematoxylin and Eosin staining, ×4 objective) and parenchyma (i: Hematoxylin and Eosin staining, ×10 objective, j: Hematoxylin and Eosin staining, ×40 objective). The infiltrates consisted of a mixture of mononuclear cells, plasma cells, eosinophils and neutrophils. Massive inflammatory infiltrates around the blood vessels were seen; however, no destruction or occlusion of the vessels was observed. (k-n) A perivascular myelin pallor lesion. (k: LFB, ×10 objective). The myelin pallor lesion exhibited diminution of myelin basic protein (MBP) immunoreactivity (l: MBP, ×10 objective), while glial fibrillary acid protein (GFAP)-positive genomic astrocytes were widely observed in the lesions (m: GFAP, ×10 objective). Aquaporin-4 (AQP4) immunostaining showed patchy diminution of immunoreactivity (n: AQP4 ×10 objective). (o) Creutzfeldt cells in the cerebral white matter (×40 objective).
the results of the CSF cytokine/chemokine analysis demonstrated atypical findings. Although prototypical MS is Th1-dominant, elevation of the levels of Th2 cytokines/chemokines, such as eotaxin, IL-5 and IL-10, was observed in our patient’s pretreatment CSF. On the other hand, the levels of Th1 cytokines/chemokines, including INF-γ and IL-2, were not increased. Elevation of the IL-17 level is observed in cases of optic-spinal multiple sclerosis (OSMS) and NMO; however, this finding was not noted in our patient. The level of IL-9 is significantly increased in patients with atopic myelitis; however, this value was not elevated in our patient (17, 18).

Although MS is regarded to be a white matter disease, recent histopathological studies of early MS (25-29) have revealed lesions in the leptomeninges and gray matter to be important initial targets of the MS process. Furthermore, re-
Recent studies have extended the earlier concept of MS, namely that the inflammation observed in MS is principally mediated by CD4+ T helper cells. An association between meningeal B-cell follicles, a severe clinical course and the extent of tissue destruction in the brain was indicated in an analysis of autopsy brain tissues obtained from patients with progressive MS (30). A clinical study of rituximab, an anti-CD20 monoclonal antibody that specifically depletes B-cells in the peripheral blood, highlighted the contribution of B-cells to the pathogenesis of MS (31).

We speculate one scenario for the pathogenesis of this acute and fulminate variant explaining why the Marburg type of MS is resistant to typical MS treatment: pathogenic peripheral lymphocytes infiltrate the CNS via meningeal and parenchymal vessels, then inflammatory infiltrates around the vessels cause perivascular demyelinating lesions. Widespread, massive and continuous inflammatory infiltration into the CNS and B-T-cell interactions appear to play a role in the early progression and severity of the disease.

Our findings regarding the neuropathology and CSF cytokine/chemokine levels showed that there are differences between our case of Marburg type MS and prototypical MS. Additional accumulation of cases and data from neuropathological investigations is needed to clarify and confirm the pathogenic differences between the Marburg type and prototypic MS.

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

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