

[CASE REPORT]

A Long Interval from a Spinal Cord Lesion to a Subsequent Brain Lesion in Primary Central Nervous System Vasculitis

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Abstract:

Primary central nervous system vasculitis (PCNSV) is an uncommon vasculitis restricted to the small- and medium-sized vessels in the brain and spinal cord. Previously, only 9 cases have been reported that initially manifested as an isolated spinal cord lesion with subsequent brain involvement, where the longest interval from the onset to brain involvement was 1 year and 11 months. We herein report the case of an isolated spinal cord lesion with subsequent brain involvement appearing seven years and five months later. This case shows that brain lesions can develop after an extended interval from spinal onset in PCNSV.

Key words: angiitis, cognitive dysfunction, myelopathy, PCNSV, vasculitis

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Introduction

Primary central nervous system vasculitis (PCNSV) is an uncommon vasculitis mainly restricted to the small- and medium-sized vessels in the brain and spinal cord (1). This disorder was previously termed granulomatous angiitis of the CNS, giant-cell arteritis of the CNS, isolated angiitis of the CNS, primary angiitis of the CNS, and benign angiopathy of the CNS (1). Most recently, the 2012 revised International Chapel Hill Consensus Conference on nomenclature of systemic vasculitis proposed the disease be called PCNSV (2).

PCNSV is often diagnosed late because it lacks specific biomarkers or imaging signatures and has mostly unknown risk factors and diverse symptomatology. PCNSV involves the brain and spinal cord, but isolated spinal cord onset is much rarer than brain onset; only nine cases have been reported that initially manifested as isolated spinal cord involvement with subsequent brain involvement (3-11). The interval from the spinal cord onset to brain involvement in previous reports ranged from 2 days (8) to 1 year and 11 months (6).

We herein report a case of PCNSV confirmed by a brain biopsy. The case was misdiagnosed as isolated myelitis at the initial presentation, and brain lesions developed seven years and five months later.

Case Report

A 50-year-old Japanese man presented with a 2-month history of progressive walking difficulties and urinary retention and was admitted to our hospital. He had no relevant medical or family history.

At a neurological examination, his consciousness was clear, and his cognitive function was normal. He had bilateral lower leg muscle weakness (Manual Muscle Test grade 3/5), and he could not walk without aids. Sensations on the trunk and extremities were normal. Deep tendon reflexes were increased in both legs, with bilateral dorsiflexion plantar responses. Lhermitte's phenomenon was also positive. Blood analyses were within normal limits, including erythrocyte sedimentation rate, C-reactive protein, and angiotensin-converting enzyme. Screening for autoantibodies was negative, including aquaporin-4-IgG, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibody, anti-SS-A and -B anti-

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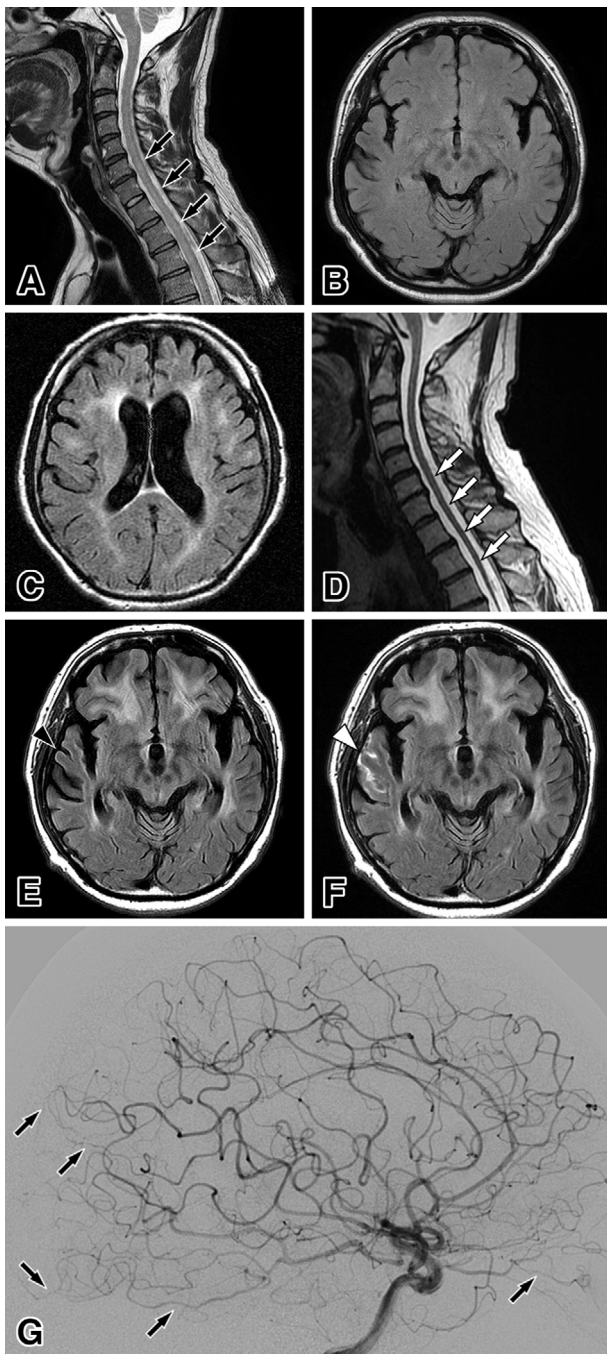


Figure 1. Radiological findings of the patient. (A, B) Magnetic resonance imaging (MRI) findings at the initial presentation. Slightly high signal intensity and swelling (black arrows) on spinal T2-weighted imaging (T2WI) (A). No apparent lesions on brain fluid-attenuated inversion recovery (FLAIR) imaging (B). (C, D) MRI findings at the brain lesion onset (7 years and 5 months after the initial spinal cord onset). Brain FLAIR imaging showing bilateral cerebral white matter lesions (C). Spinal T2WI showing diffuse atrophy from the cervical area to the thoracic cord (white arrows) (D). (E, F) MRI findings at the time of the biopsy (8 years and 2 months after the initial onset). Brain FLAIR imaging revealing high signal intensity (E; black arrowhead) with gadolinium enhancement (F; white arrowhead) at the right temporal lobe. Digital subtraction angiography showing focal stenoses at the distal portion of the cerebral arteries (arrows), suggesting vasculitis (G).

body, and anti-DNA antibodies. Screening for infectious diseases was normal, including syphilis serology, hepatitis B and C, human immunodeficiency virus and human T-cell leukemia virus type 1 antibodies. Cerebrospinal fluid (CSF) showed pleocytosis with 59 cells/ μ L (57 mononuclear cells) and an elevated protein level of 97 mg/dL, and oligoclonal bands were positive. CSF polymerase chain reaction analyses were negative in herpes viruses (herpes simplex virus, herpes zoster virus and Epstein-Barr virus). CSF cytology showed no malignant cells. Spinal T2-weighted magnetic resonance imaging (MRI) revealed a slightly high signal and swelling through the cervical area to the thoracic spinal cord (Fig. 1A). Brain MRI revealed no lesion at that time (Fig. 1B). He was thus diagnosed with myelitis of unknown cause and treated with intravenous methyl-prednisolone, followed by oral prednisolone. With treatment, he could walk independently, but his spastic gait remained, so the administration of prednisolone was discontinued for three years. His walking difficulty gradually worsened, and he began using a wheelchair at seven years and five months after the first onset. At that time, he showed an altered mental status, which included incoherent conversations and mild cognitive decline, and he could not text-message his wife. A neurological examination revealed mild disorientation. The muscle strength was normal in the upper limbs but was totally impaired in lower limbs. His Mini-Mental State Examination (MMSE) score was 13/30. Brain MRI showed periventricular bilateral cerebral white matter lesions but no enhanced lesions at that time (Fig. 1C). Spinal MRI showed diffuse atrophy of the spinal cord without enhanced lesions (Fig. 1D). He was treated again with steroid therapy under the diagnosis of encephalomyelitis.

His cognitive function recovered within a month; his MMSE score was 24/30, he was able to text-message his wife again, and his spasticity diminished. Oral prednisolone was ended six months after the initiation of the therapy. However, one month after the end of prednisolone, his cognitive function deteriorated again. His MMSE score was 19/30. Brain MRI showed fluid-attenuated inversion recovery (FLAIR) high-intensity lesions in the right temporal lobe (Fig. 1E) with gadolinium enhancement (Fig. 1F). Digital subtraction angiography revealed multiple focal stenosis in the distal portion of the cerebral arteries (Fig. 1G); no other abnormalities were found in the systemic vessels. An open biopsy from the right superior temporal gyrus was performed to confirm the diagnosis.

Histologically, inflammatory cells infiltrated within and around the walls of the small- to medium-sized vessels in the cerebral cortex (Fig. 2A). The lumen of the leptomeningeal and parenchymal vessels showed marked stenosis with hyalinous thickening of the wall (Fig. 2B). Hyalinotic changes of the vessel walls were evident with phosphotungstic acid staining, and they were more prominent in the leptomeningeal vessels than in the parenchymal vessels (Fig. 2C). Atrophic neurons in the cerebral cortex indicated ischemia, but there was no evidence of infarction. Immuno-

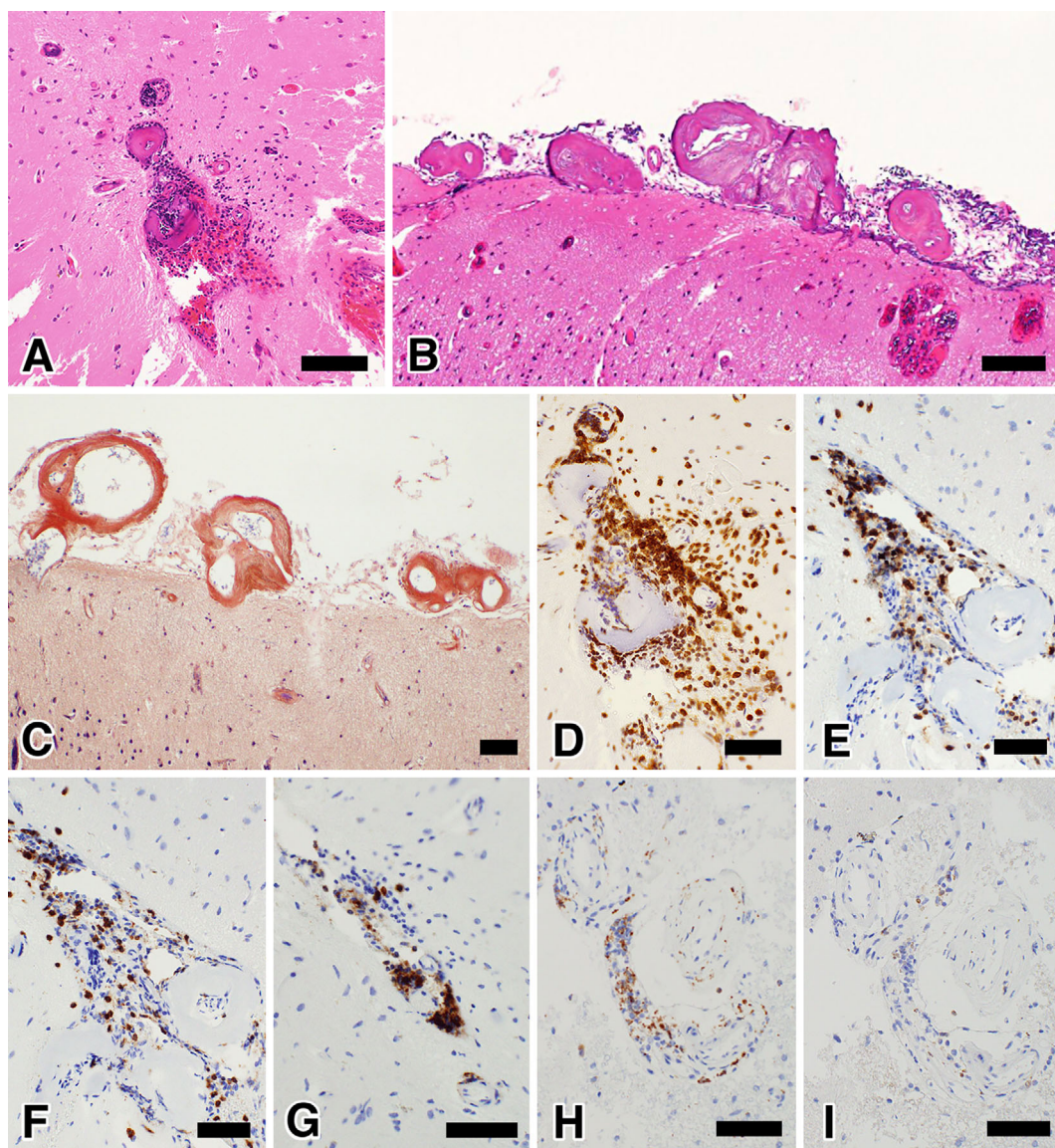


Figure 2. Histopathological findings. Inflammatory cells infiltrating within and around the walls of small- to medium-sized vessels in the cerebral cortex (A). Hyalinous thickening and stenosis in the leptomeningeal and parenchymal vessels (B). Evident hyalinotic changes of the vessel walls with phosphotungstic acid staining, more prominent in the leptomeningeal vessels than in the parenchymal vessels (C). Infiltrated inflammatory cells: mostly CD45-positive (D), predominantly CD3- (E), CD8- (F) and CD20-positive (G), CD68-positive in a small proportion (H), CD4-positive in a few cells (I). Hematoxylin and Eosin stain (A, B). Bars, 100 μ m (A, B) and 20 μ m (C-G).

histochemically, amyloid β was negative in the vessel walls (data not shown). Infiltrated inflammatory cells were mostly CD45-positive, indicating these cells were T lymphocytes (Fig. 2D). The infiltrated cells were predominantly CD3-, CD8- and CD20-positive (Fig. 2E-G), and a small proportion were CD68-positive (Fig. 2H). CD4 stains showed faint immunoreactivity (Fig. 2I).

A diagnosis of PCNSV was made according to the criteria suggested by Calabrese and Mallek (12) and Birnbaum and Hellmann (13). Steroid therapy and cyclophosphamide (50 mg/day) were given to the patient, and his cognitive impairment recovered within 2 weeks; his MMSE score was 29/30. A combination of steroid and cyclophosphamide therapy was continued, and clinical and radiological relapse has

not been seen for up to three years.

Discussion

We encountered a case of PCNSV that had a long interval between the initial isolated spinal cord onset and the subsequent brain involvement.

PCNSV can manifest as a purely brain or spinal cord event or with concomitant brain and spinal cord involvement. Spinal cord involvement has been documented much less frequently than brain involvement; approximately 5% of patients with PCNSV have spinal cord involvement (11). Spinal cord involvement may develop initially along with brain manifestations or may occur earlier or later in the

course (14). Few cases have developed brain and spinal cord lesions simultaneously (11, 15, 16). Only nine previous cases with an initial manifestation as an isolated spinal cord lesion and subsequent brain involvement have been reported (3-11). Seven of these nine cases had an altered mental status later in the course of the isolated spinal onset; our case was misdiagnosed with encephalomyelitis when the patient presented with an altered mental status. The longest interval from the spinal cord onset to brain lesions among previously reported cases was 1 year and 11 months (6). The interval in one of the nine cases was not reported, but the patient died within eight months after the initial spinal onset (17). The interval between the spinal onset of PCNSV and symptoms of the brain in the present case was seven years and five months, which is the longest interval among the reported cases. Our case was administered steroid therapy for three years before the brain manifestation. Steroid therapy was also administered in several previous cases (6, 7, 9, 10, 17), but all previous cases were given steroids for a short duration. This might be the reason why our case had the longest interval until brain lesions appeared.

PCNSV histologically affects small- and medium-sized leptomeningeal and parenchymal arterial vessels. Three main histopathological patterns are seen: granulomatous, lymphocytic and necrotizing vasculitis (14). Granulomatous vasculitis is the most common, showing mononuclear inflammation and granulomas with multinucleated giant cells. Lymphocytic vasculitis is the second-most common pattern, where lymphocytic inflammation predominates. Necrotizing vasculitis is the least common pattern and is characterized by transmural fibrinoid necrosis. Amyloid deposition is seen with the granulomatous pattern, called A β -related angiitis, but is rarely noted in specimens with non-granulomatous PCNSV. These histological patterns are not considered to be closely linked to specific clinical manifestations, treatment responses or outcomes (14). In the present case, the infiltrated inflammatory cells were mostly lymphocytes and were seen within or around vascular walls. Furthermore, amyloid β was negative in the vascular walls. Therefore, the type of histological pattern appeared to be a lymphocytic vasculitis pattern. Immunohistochemically, the infiltrated lymphocytes of the present case were mostly CD45-, CD3-, CD8- and CD20-positive and scarcely CD68- and CD4-positive. Consistent with these findings, the three above-mentioned histological types of PCNSV cases have all been reported to be CD45-, CD68-, CD8- and CD20-positive (18-25). Based on these findings, cytotoxic T lymphocytes and humoral immunity may be associated with the pathogenesis of PCNSV. However, the relationship among CD clusters, histological types and clinical phenotypes does not appear to be specific.

In conclusion, the findings in the present case suggest that neurologists should consider PCNSV when a patient develops brain lesions even after an extended interval from the first spinal onset in patients with a pure spinal cord lesion.

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

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