

Primary angitis of the central nervous system with myelopathy as initial clinical presentation

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Abstract

Primary angitis of the central nervous system (PACNS) is a rare vasculitis restricted to the central nervous system without systemic involvement. Delay in diagnosis and treatment is common due to its non-specific symptoms and lack of non-invasive diagnostic tests. Myelopathy can occur in PACNS, during the clinical course of the illness, with or without cerebral symptoms. We describe here a 51 year-old ethnic Chinese woman who presented initially with paraparesis without cerebral symptoms. The diagnosis of PACNS was eventually made from brain biopsy when she subsequently developed cerebral involvement. Despite aggressive treatment, the patient developed progressive neurological deterioration and died. This patient demonstrates the rare occurrence of myelopathy as the sole initial presentation of PACNS.

INTRODUCTION

Primary angitis of the central nervous system (PACNS) is a rare and life-threatening disease secondary to inflammation of blood vessels in the brain and spinal cord.¹ It has been reported that PACNS may rarely present with spinal symptoms.² Salvarani *et al.* reported 101 PACNS patients followed up in the Mayo clinic over 21 years. Five patients (5%) had spinal cord involvement.³ Myelopathy was the initial manifestation for three patients; however, two of the three also had simultaneous cerebral vasculitis. In one patient, spinal cord involvement was the only manifestation at presentation. Thus, it is rare for PACNS to have spinal cord vasculitis as the only initial manifestation. We report here a patient with PACNS, who presented with spinal cord symptoms, and later developed cerebral symptoms. The diagnosis was established eventually by brain biopsy.

CASE REPORT

A 51-year old ethnic Chinese woman presented with acute urinary retention in January 2012. She did not have lower limb weakness and her mentation was normal. She was investigated in another hospital, where a brain MRI demonstrated T2-hyperintensity in the white matter of both posterior parietal lobes, left more than right. Her symptom was attributed to a stroke. She

was discharged home with intermittent self-catheterisation.

A month later, she experienced progressive both lower limbs weakness which rendered her wheelchair-bound by April 2012. Examination then showed bilateral flaccid paraparesis with normal upper limbs and cognition. An MRI of the spine revealed T2 hyperintense lesions over T2-T4, T7-T10 and T12-L1 (Figure 1a). Another brain MRI showed that the T2/FLAIR hyperintense lesions of the deep white matter in the posterior parietal lobes have increased in size, extending to the left frontal lobe, with restricted diffusion on DWI/ADC sequences. There was sparing of the subcortical region. CSF oligoclonal IgG band was positive. She was diagnosed as a case of long thoracic cord transverse myelitis and treated with intravenous methylprednisolone.

Four months after the initial presentation, she developed confusion and was seen in our centre. There was no history of fever, headache or seizure. Neurological examination showed that she was confused, mute, had blank stares at most times, and could not obey oral commands. She refused oral intake. There was flaccid paraplegia, with absent tendon reflexes and plantar responses. Upper limb examination was normal. The anal sphincter tone was lax.

Further investigations including blood count, renal, liver and thyroid function tests, calcium, hepatitis B and C, VDRL and HIV



Figure 1: (a) MRI spine; T2W (sagittal). Long segment intramedullary high signal intensities over the T2-T4, T7-T10 and T12-L1 of the spinal cord (black arrows). (b-c) Whole spine MRI post gadolinium sagittal T1W images. Patchy areas of enhancement are seen in the upper, mid and lower thoracic spinal cord.

antibody, C-reactive protein were all normal or negative. There was raised erythrocyte sedimentation rate of 47 mm/hour. Connective tissue disease tests including complement levels, antinuclear antibody, extractable nuclear antibody, anticardiolipin antibody, rheumatoid factor, serum immunoglobulin, antineutrophil cytoplasmic antibody (ANCA), N-methyl-D-asparaginase receptor (NMDAR) antibody, voltage-gated potassium channel (VGKC) antibody; tumor markers, serum JC virus PCR were all negative. CSF examination revealed slight pleocytosis (4 cells/ μ L), elevated protein (1.52 g/L) and normal glucose. Bacterial culture, acid fast bacilli and cytological examination were negative. CT thorax, abdomen, and digital cerebral angiography were also normal. Electroencephalography (EEG) showed excessive diffuse slowing.

Compared to the initial previous scans, the repeat brain MRI at 6th month of illness showed progression of the T2/FLAIR hyperintense lesions in the white matter extending from both parietal to both temporal, left frontal and both cerebellar hemispheres with involvement of the grey matter (Figure 2a-f). There was gyriform T1W hyperintensity over both posterior parietal

indicating cortical laminar necrosis. The repeat spinal MRI showed patchy Gad-enhancing lesions over multiple level of thoracic cord at T1-T5, T7-T10 and T12-L1 (Figure 1b-c). A second course of methylprednisolone was given; however, there was no significant clinical improvement.

Seven months after the onset of symptoms, a brain biopsy was performed. The histopathology examination showed cerebritis and necrosis with diffuse infiltration of chronic inflammatory cells predominantly foamy histiocytes and lymphocytes. A meningeal vessel showed intramural infiltration by mononuclear chronic inflammatory cells (Figure 3). There was no evidence of intravascular malignant cells or lymphoma. The patient was diagnosed to have PACNS.

CSF examination repeated showed elevated protein of 4.23 g/L, normal glucose and no cells. She was treated with two cycles of monthly pulsed cyclophosphamide and oral prednisolone. There was no improvement. She developed intractable seizures, and a repeat MRI brain showed multilobar haemorrhages over the left occipital, both parietal, right frontal and left insular cortex. She died from sepsis, 12 months after initial symptoms. No post-mortem was done.

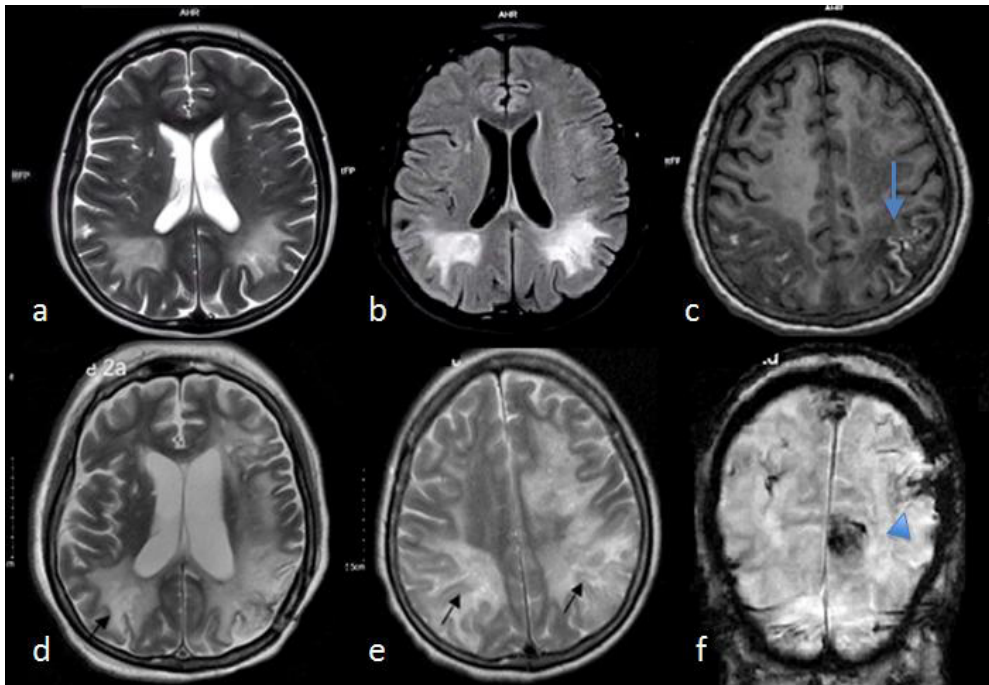


Figure 2: (a-b) Brain MRI (Axial T2W and FLAIR) during initial presentation. Bilateral almost symmetrical confluent high signal intensities over the deep white matter of both posterior parietal lobes with sparing of the subcortical ‘U’ fibers. (c) Follow up MRI; Axial T1W. Gyral hyperintensity in the posterior parietal lobes in keeping with laminar cortical necrosis (blue arrow). (d-e) Areas of high signal changes (black arrows) in both cerebral lobes predominantly posterior parietal and occipital lobes affecting the periventricular and deep white matter. (f) Coronal gradient echo (GRE*) showing hypointense blooming artefacts in both posterior parietal and occipital lobes consistent with foci of haemorrhage (blue arrowhead).

DISCUSSION

This patient was diagnosed to have PACNS based on progressive multifocal involvement of CNS, histopathological evidence of CNS vasculitis of the meningeal vessels wall, absence of systemic vasculitis and exclusion of other differential

diagnoses. This patient presented with acute urinary retention and followed by progressive paraparesis from spinal cord involvement. This was confirmed by the spinal MRI (Figure 1). Although the initial MRI brain had mild changes in the posterior parietal white matter, this did not correlate with the presenting symptom. She only

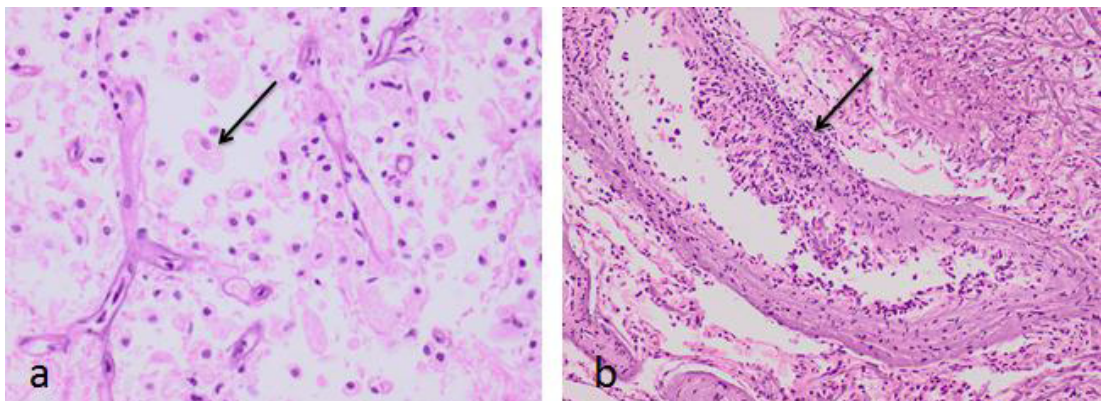


Figure 3: (a) Cerebral necrosis and infiltration by mainly foamy macrophages (arrow) and lymphocytes. (b) Focal segmental, intramural inflammation of a meningeal vessel (arrow) consistent with vasculitis. H&E stains; magnification, x100 objective (a); x40 objective (b).

Table 1: Summary of clinical features, treatments and outcomes of patients presenting with myelopathy from PACNS in the literature

Case	Age (yr)/ Sex	Symptoms related to SC involvement	Myelitis only	Time between SC and cerebral symptoms	Myelography/Myelo-CT/MRI spine	Pathology specimen	Treatment	Outcome (reference)	Follow up period
1	26/F	LE weakness	-	ND	ND	Autopsy	None	Died of fatal ICH (4)	24 months
2	50/M	LE weakness and numbness; bladder incontinence	-	ND	ND	Autopsy	None	Died of cerebral manifestations of PACNS (5)	6 weeks
3	21/M	LE weakness and numbness	-	ND	Myelography: abnormal flow of dye	Autopsy	Steroid	Transient neurological stabilization with steroids; relapse and death from ICH (6)	34 months
4	76/M	Acute transverse myelitis	Yes	N/A	ND	Autopsy	ND	ND (7)	ND
5	57/F	Progressive spastic quadripareisis	Yes	N/A	ND	Autopsy	None	Death (8)	9 months
6	47/M	LE weakness and numbness; bladder incontinence	-	SC symptoms occurred 11 months earlier	Cervical & lumbar myelogram: irregularity of the cauda equina and arachnoid	Autopsy	Steroid	No response to steroids; death from cerebral manifestations of PACNS (9)	23 months
7	21/M	LE weakness and numbness	-	ND	ND	Autopsy	Steroid	Transient stabilization of disease; relapse and death from ICH (10)	24 months
8	44/M	LE weakness and numbness; bladder incontinence	Yes	N/A	ND	Cord biopsy	Steroid+CYC	Stabilization of disease after adding cytotoxic agent (11)	+
9	33/M	Progressive paraparesis	Yes	N/A	ND	Autopsy	Steroid+NM	No response (12)	>5 months
10	43/M	LE weakness and numbness; bladder incontinence	-	SC symptoms occurred 12 months earlier	ND	Brain biopsy	Steroid+CYC	Improved after combination with CYC (13)	+
11	64/F	LE weakness; urinary incontinence	-	SC symptoms occurred 5 months earlier	CT myelogram: elliptical intramedullary enlargement of conus medullaris	Brain biopsy	Steroid+CYC	Improvement with residual paraparesis (14)	12 months
12	28/M	LE weakness; incontinence	-	ND	ND	Autopsy	Steroid	Transient improvement with steroids then relapse and death from cerebral manifestations of PACNS (15)	9 months

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Case	Age (yr)/ Sex	Symptoms related to SC involvement	Myelitis only	Time between SC and cerebral symptoms	Myelography/Myelo-CT/MRI spine	Pathology specimen	Treatment	Outcome (reference)	Follow up period
13	28/M	LE weakness and numbness; bladder incontinence	Yes	N/A	ND	Cord biopsy	Steroid of PACNS (15)	No improvement in neurological status with steroids; subsequent development of Hodgkins disease (16)	+
14	62/M	Progressive quadripareisis and ataxia; cervical myelopathy	Yes	N/A	ND	Cord biopsy	Steroid	Recovery after steroid therapy (17)	+
15	31/M	Progressive spastic paraplegia, sensory changes and bladder incontinence	Yes	N/A	ND	Autopsy	None	Progressive weakness; death (18)	ND
16	12/M	LE weakness and numbness; bladder incontinence	Yes	N/A	MRI spine: Gad enhanced T1W, enlargement of lower thoracic & lumbar cord extended from T7 to conus	Cord biopsy	Steroid	Partial neurological recovery with steroids; stabilization of disease at 6-month follow up (19)	6 months
17	28/M	LE weakness and numbness; urinary incontinence	-	SC symptoms occurred 2 months earlier	MRI spine: Increased T2W signal within the cord at C1-2 and T2-3 and within the conus	Autopsy	Steroid+CYC	Death (20)	5 months
18	52/F	LE weakness and numbness; saddle anaesthesia	Yes	N/A	MRI spine: enlarged conus, increased signal T2W & irregular Gad enhancement extending from T11 to L1	Cord biopsy	Steroid+CYC	Significant recovery with minimal residual sensory deficit (21)	36 months
19	46/M	LE numbness; progressive paraparesis; neurogenic bladder	-	SC symptoms occurred 10 months earlier	MRI spine: abnormal T2W signal, mild expansion & enhancement of low thoracic cord, conus& cauda	Cord biopsy	Steroid	Transient improvement with mild relapse when steroid tapered (3)	22 months
20	44/F	Progressive paraparesis with sensory loss below C5	Yes	N/A	MRI spine: Gad enhancement posterior part of cord with intramedullary edema, extended from C2-C7	Cord biopsy	Steroid+ MTX	Recovery (22)	24 months

* SC, spinal cord; LE, lower extremity; N/A, not applicable; ND, no data; ICH, intracranial haemorrhage; CYC, cyclophosphamide; NM, nitrogen mustard; AZA, azathioprine; MTX, methotrexate; +, patient survived but duration unknown

had mental symptoms 4 months later.

As mentioned above, it is rare for PACNS to present with spinal cord symptoms as the only manifestation as in our patient. We reviewed the English literature from 1922-2010 and found 20 cases of PACNS with spinal cord involvement, mainly derived from small series or individual case reports (Table 1). The age of these patients ranged from 12 to 76 years (mean, 40.7 years). Three quarters (15) of the patients were males. Ten cases (50%) did not develop cerebral manifestation during the period of follow up. However, in 5 of the cases, the follow up period was not known. The follow up period was less than a year in 3 other cases. Two patients had only myelitis at 24 months and 36 months follow up²¹⁻²², suggesting that “isolated spinal cord vasculitis” may persist in rare occasion. In the remaining 10 cases, the cerebral symptoms occurred 2 to 12 months later. In all the cases, the diagnosis was established by histopathological examination from 11 autopsy, 7 cord biopsy and 2 brain biopsy.

As for prognosis, it appeared to be poor overall, particularly those that subsequently developed cerebral involvement.^{8,18} Of the 20 cases, 8 cases showed stabilization of disease with improved neurological deficits. Of these, only 3 patients had subsequent cerebral involvement. For the remaining 12 patients, 9 died from the primary angiitis, with 7 patients developed cerebral involvement. Two patients had no improvement and 1 with no further detail. The initial spinal cord involvement may have contributed to delays in diagnosis and treatment, and thus contribute to the poor prognosis.^{11,23}

In conclusion, we presented a case of PACNS with initial spinal cord manifestation as sole symptoms. PACNS should be included in the differential diagnoses of a patient presenting with transverse myelitis.

DISCLOSURE

Conflict of interest: None

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