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Clinical characteristics of patients with paraneoplastic myelopathy

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ABSTRACT

Paraneoplastic myelopathy is rare paraneoplastic neurological syndromes. We reviewed patients through medical records system and screened patients who presented with myelopathy, and/or coexisting cancer, and/or onconeural antibodies. Nine patients were identified as paraneoplastic myelopathy presenting with progressive subacute (2/9) or insidious (7/9) myelopathy. CSF abnormalities included elevated protein, 5; pleocytosis, 4; excess oligoclonal bands, 6. Seven patients had onconeural antibody. Cancer was confirmed histopathologically in 6 and diagnosed by PET-CT in 1. Four patients had symmetric, longitudinally extensive grey matter or tract-specific changes on spinal cord MRI. It was associated with significant morbidity and had poor response to treatment.

1. Introduction

Paraneoplastic neurological syndromes (PNSs) are serious and rare autoimmune disorders that occur in approximately 0.01% of patients with cancer (Dalmur and Rosenfeld, 2008). Though PNS can affect any part of the nervous system, paraneoplastic myelopathy is extremely rare compared with the well-charatererized limbic encephalitis, paraneoplastic cerebellar degeneration, Lambert-eaton myasthenia syndrome and paraneoplastic neuropathies. It only accounts for nearly 6.5% of the overall PNSs (Giometto et al., 2010). The pathogenesis of PNS is associated with immune cross-reactivity of antibodies against antigens expressed by tumour cells and the neurological system (Albert et al., 1998). Its occurrence is rare but increasing with improved recognition of the disease and early detection of onconeural antibodies. Early recognition of all these diseases is crucial as it may lead to the detection of occult cancer. Here we report the clinical characteristics and outcomes of paraneoplastic myelopathy.

2. Patients and methods

To identify cases of paraneoplastic myelopathy, we retrospectively reviewed patients through the medical records system of Xuanwu Hospital, Beijing, China, between January 2010 and December 2017 using the keywords progressive myelopathy, subacute myelopathy, paraneoplastic myelopathy and paraneoplastic neurological syndromes. Then we screened the patients who presented with myelopathy, and/or coexisting cancer, and/or onconeural antibodies. The diagnosis was made based on consensus guidelines by Graus et al. for the diagnosis of PNS (hereinafter, the Graus criteria) (Graus et al., 2004).

2.1. Clinical evaluation

Patient clinical characteristics included sex, age, neurological and systemic symptoms at the time of disease onset, interval from onset to diagnosis, interval from onset to wheelchair dependence, treatment and follow-up time. Besides, lab findings, spinal magnetic resonance imaging (MRI), photon emission tomography (PET), and the other tests included in the ultrasonic and radiologic screening for a systemic neoplasm were reviewed.

2.2. Laboratory findings

All patients underwent a full laboratory tests which included complete blood cell count, hepatic and renal function, thyroid hormone levels, urinalysis, tumour markers, angiotensin-converting enzyme, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies and rheumatic factor, serum immunoelectrophoresis and immunoglobulin studies, serum and CSF AQP4 antibody and onconeural autoantibodies, CSF flow cytometry and cytopathology.

The onconeural autoantibodies, including antineuronal nuclear autoantibody (ANNA−1, anti-Hu), ANNA-2 (anti-Ri), Purkinje-cell

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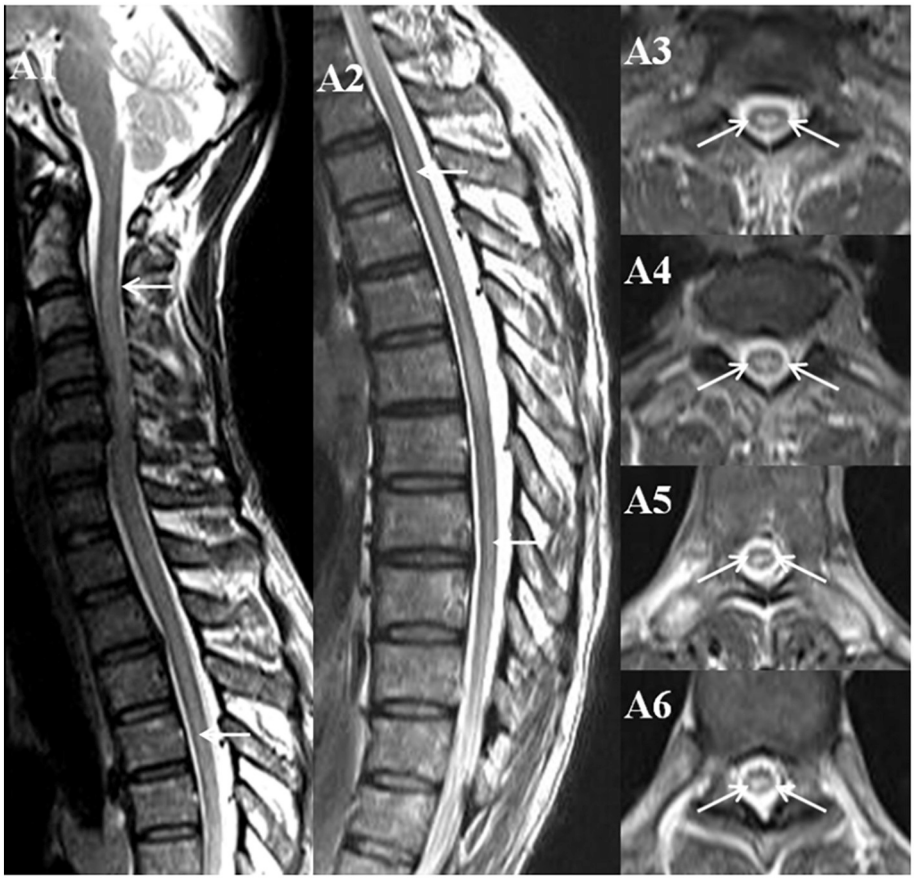

Fig. 1. MRI cervical and thoracic spine images from patient 1. Patient 1 had longitudinally extensive T2 signal abnormality extending across 18 spinal segments (A1, A2) that symmetrically involved the central grey matter on axial T2-weighted images (A3, A4, A5, A6).

cytoplasmic autoantibody type 1(PCA-1, anti-Yo), collapsin response-mediator protein 5–immunoglobulin G (IgG) (CRMP-5), amphiphysin-IgG, Glutamic acid decarboxylase 65 (GAD-65), and Ma2(anti-Ta), were assessed by the indirect immunofluorescence test on serum or CSF (Storstein and Vedeler, 2007). Serologic evaluation for anti-AQP4 antibody (AQP4-Ab) by cell-based assays was undertaken (Takahashi et al., 2006).

2.3. Imaging

Magnetic resonance imaging of the brain, cervical and thoracic sections of the spinal cord, including T1-weighted, T2-weighted, and gadolinium-enhanced T1-weighted imaging, was performed on all patients. Whole-body PET scan was performed in 2 patients.

2.4. Differential diagnosis

Extensive examinations were done to exclude competing diagnoses, including progressive myelopathy such as neurosarcoidosis (which did not fit the diagnostic criteria (Zajicek et al., 1999; Flanagan, 2016), primary or metastatic neoplastic myelopathy (patients with spinal lesions were evaluated by PET (Flanagan et al., 2012; Flanagan et al., 2011a, 2011b, 2011c), other inflammatory myelopathy such as neuromyelitis optica (NMO) (progressive NMO clinical course is rare (Wingerchuk et al., 2015) and progressive solitary sclerosis (Keegan et al., 2016), compressive myelopathy (Flanagan et al., 2014), infectious myelopathy, nutritional myelopathy, toxic myelopathy and inherited spastic paraparesis. For patients with negative onconeural antibodies, spinal vascular malformations, especially spinal dural arteriovenous fistulas (AVF), is needed to pay attention, which may present as progressive myelopathy with 0.5 months to 3 years duration (Ma et al., 2018). Case 6 had spinal vascular angiography to exclude the possibility of spinal dural AVF.

2.5. Ethics approval

This study was approved by the ethics committee of the Xuanwu hospital of the Capital Medical University, and all patients consented to the use of their medical record for research purposes. Informed consent was obtained from all individual participants included in the study.

3. Results

3.1. Patient's diagnosis

Nine patients were identified as paraneoplastic myelopathy through the screening. Paraneoplastic myelopathy belongs to non-classical paraneoplastic neurological syndrome (Graus et al., 2004). According to the Graus criteria, seven patients were diagnosed as definite PNS (a non-classical syndrome with onconeural antibodies and cancer, CRMP-5 + small-cell lung carcinoma [SCLC], 1; anti-Ri + breast carcinoma, 1; anti-Hu + SCLC, 1; anti-Hu + colon carcinoma, 1; anti-Hu + SCLC, 1; a neurological syndrome, classical or not, with well characterized onconeural antibodies and no cancer, amphiphysin, 1; anti-Yo, 1), and two possible PNS (chronic progressive myelopathy + renal cell carcinoma, 1; chronic progressive myelopathy + SCLC, 1).

3.2. Clinical and demographic features

All nine patients presented with a progressive myelopathy of either

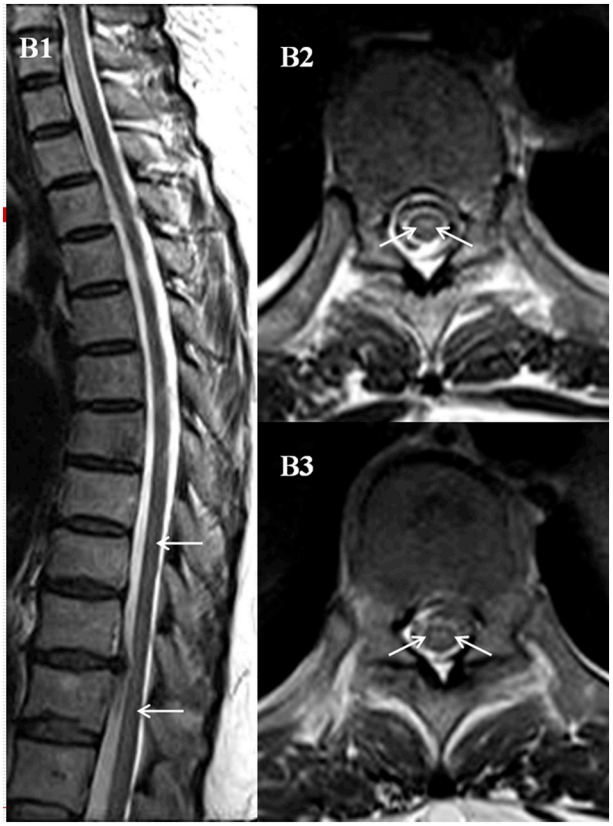

Fig. 2. MRI thoracic spine images from patient 2. Patient 2 had longitudinally T2 signal abnormality extending from T10 to T12 spinal segments (B1) that symmetrically involved the central grey matter on axial T2-weighted images (B2, B3).

subacute (2/9) or insidious onset (7/9) with a median follow-up of 16.5 months (range 1.5 to 49 months). Symptoms evolved progressively in all patients; 40% were wheelchair bound at 6 months after symptom onset. Four (4/9) were female. The median age at the onset of symptoms was 61 years (range 46–71 years). Regarding the clinical manifestations, six of the nine patients presented with isolated myelopathy, and two patients developed symptoms of peripheral neuropathy concurrently, and one patient had combined stiff-person syndrome.

3.3. CSF features

Cerebral spinal fluid (CSF), analysed in eight patients (89%), was found to be abnormal in 7 (88%) of the cases, lymphocyte-predominant pleocytosis in 4 (50%: median leukocyte number/L 27; range 13–102; normal 0–5), elevated protein concentration in 5 (63%: median 138 mg/dL; range 60–188; normal 15–45), and excess oligoclonal bands (OCB) in 6 of 8 (75%). An onconeural autoantibody was detected in eight patients (89%), and seven of eight patients had one onconeural antibody (amphiphysin, 1; CRMP-5, 1; anti-Hu, 3; anti-Yo, 1; anti-Ri 1). All sera tested were negative for aquaporin-4 IgG. Cancer was confirmed histopathologically in 6 patients (67%) and diagnosed by PET-CT in 1 patient (11%). Myelopathy preceded cancer detection in 6 (67%; the median time to cancer detection, 11 months [1.5–19]).

3.4. Neuroimaging findings

Spinal MRIs (cervical and thoracic, 9) revealed T2 signal abnormalities in 4 patients (4/9) (Figs. 1, 2, 3 and 4). Four patients had longitudinally extensive signal abnormality (≥3 vertebral segments; median 5.25 segments). Four patients had symmetric and tract or grey matter confined T2 signal abnormality, in the following distributions: lateral column, 1; dorsal column, 1; central grey matter, 2. Spinal lesions showed a slight gadolinium enhancement in only one patient

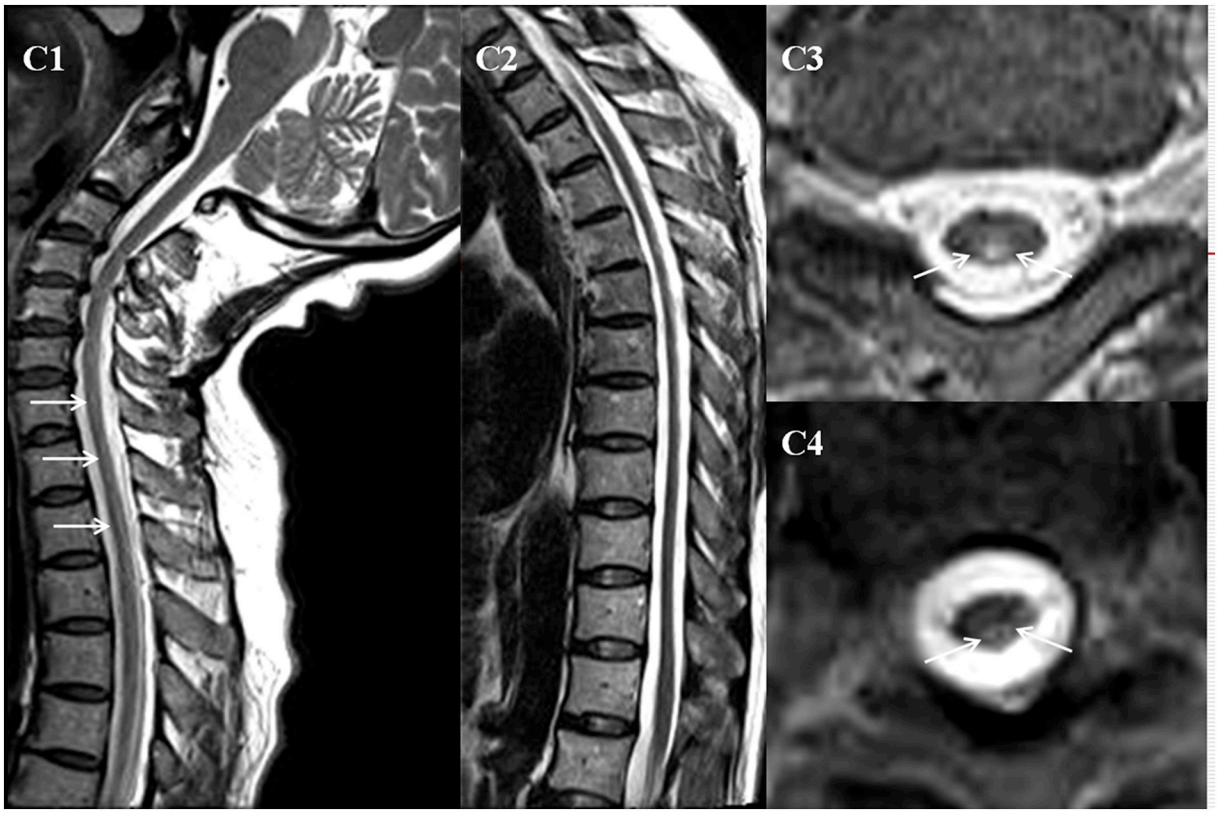

Fig. 3. MRI cervical and thoracic spine images from patient 3. Patient 3 had longitudinally extensive T2 signal abnormality in T1 to T6 dorsal spinal cords (C1) in addition to diffused cord atrophy and distorted spine due to stiff-person syndrome. There were symmetric abnormality in the dorsal column region on axial images (C2, C3).

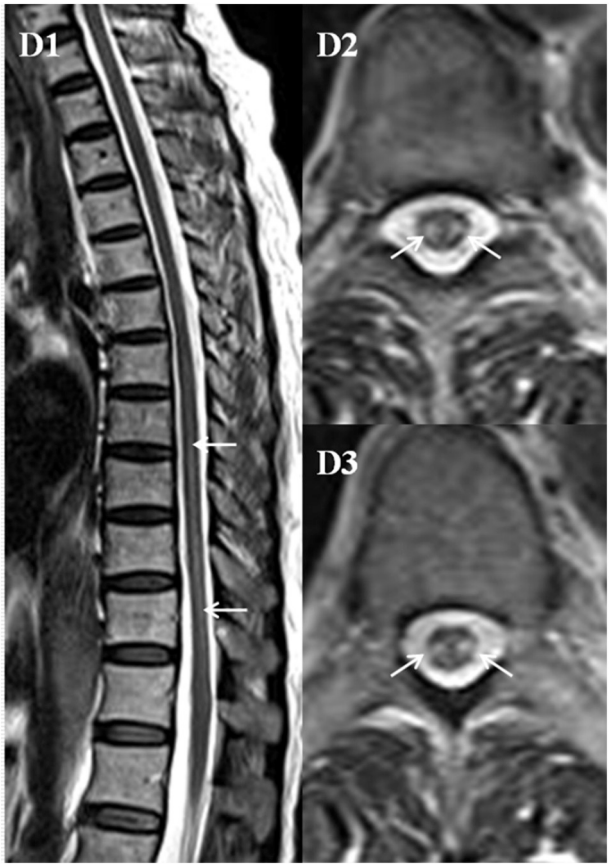

Fig. 4. MRI thoracic spine images from patient 4. Patient 8 had longitudinally extensive tract-specific T2 signal abnormality on the sagittal section extending across 4 segments from T8 to T11 (D1) with symmetric involvement of the lateral columns (D2, D3).

(case1). Whole-body PET scans were performed in five patients, and revealed cancer in four. None had spinal cord hypermetabolic foci. Brain MRIs performed in all nine patients showed no lesions with MS characteristics.

3.5. Treatment and prognosis

Eight patients received immunotherapy (1, case 3), cancer treatment (3, case 1, 4, 7), or both (4, case 2, 5, 6, 9). Cancer treatments included surgery for 6 (1, 2, 4, 5, 6, 7) and chemotherapy for 3 (2, 5, 9) (combination in some cases). The duration from myelopathic symptom onset to the beginning of immunotherapy was 40 months in case 3, 7 months in case 5, 19 months in case 6 and 1 month in case 8 (range 1–40 months). None of the patients showed clinical improvement. Case 5 and case 9 were stable on follow-up. Case 2, 3, 4, 6 and 8 deteriorated. Case 1 and case 7 died 24 and 23 months after the onset of myelopathy.

Table 1 summarises the clinical, serologic, CSF, oncologic and radiologic characteristics for the nine identified patients.

4. Discussion

Paraneoplastic myelopathies are rare but important categories of spinal cord diseases to recognise, because the neurologic signs often precede the diagnosis of cancer. None of our nine patients had a previous neoplastic history when they came for diagnosis of myelopathy, but carcinoma was detected in seven of them and was treated at the earliest opportunity. Our patients had chronic or subacute onsets, six of them presented with isolated myelopathy, one presented with myelopathy and stiff-person syndrome, two of them had combined neuropathy. Paraneoplastic myelopathies belong to autoimmune myelopathies (Flanagan, 2016), and are caused by an immune-mediated damage of the spinal cord in patients with systemic tumours. Pleocytosis and unique ologoclonal bands on CSF examinations, gadolinium-enhanced lesions on MRI and onconeural antibodies in serum, support the inflammatory nature of paraneoplastic myelopathies. In a European study, pleocytosis was found in 39% of the PNSs cases, elevated proteins in 67% and OCB in 63% (Psimaras et al., 2010). In Flanagan et al. ‘s study, lymphocyte pleocytosis was revealed in 63% of the cases with isolated paraneoplastic myelopathy, elevated protein levels in 92% and excess OCB in 30% (Flanagan et al., 2011b). In our case series, 8 patients (89%) fulfilled CSF examinations. Lymphocyte pleocytosis was discovered in 4 (50%) of the cases, elevated protein concentration in 5 (63%), and unique OCB in 6 (75%). In Psimaras et al.'s study on CSF in PNSs, they found that pleocytosis was detected in 47% of patients before the third month from onset of PNSs compared with 28% after the third month (Psimaras et al., 2010). In our cases with CSF pleocytosis, the mean time from onset of myelopathy was 4.1 months (range 1–7 m), whereas it was 18.5 months for those with normal cell numbers in CSF. This might support the opinion that a subacute inflammation is followed by a non-inflammatory phase in the development of paraneoplastic myelopathy.

Though amphiphysin-IgG and CRMP-5-IgG are the two most common onconeural autoantibodies associated with paraneoplastic myeloapthy (Flanagan et al., 2011c), our patient series had diversified onconeural antibodies including anti-Hu, anti-Ri and anti-Yo. In addition, a variety of antibodies, including ANNA-3, PCA-2, Ma1 and Ma2, may be associated with isolated myelopathy or myelopathy in the setting of a multifocal neurologic symptoms (Graus et al., 2010). The antibodies typically target intracellular antigens and are therefore more likely a marker of a related CD8+ cytotoxic T-cell response than directly pathogenic. Paraneoplastic autoantibodies are detected in approximately 81% of patients with paraneoplastic isolated myelopathy (Flanagan et al., 2011c). In the European multicenter study, 81.7% of patients with definite PNSs harboured onconeural antibodies (Giometto et al., 2010). In our series, seven of eight patients had one onconeural antibody, with a similar positive ratio to the above studies. It is unknown why no antibodies were found in some patients and may be related to unidentified antibodies. Our patient who had no onconeural antibodies detected had renal cell carcinoma. Johnson et al. reported a patient presenting with progressively worsening gait difficulty and renal cell carcinoma, who had negative “well-characterized” paraneoplastic antibodies but positive biotinylated serum analysis for hippocampal and cerebellar Purkinje cells (Johnson et al., 2008).

International guidelines recommend that patients with a high suspicion of PNSs, but without detectable onconeural antibodies, should be followed clinically and radiologically for up to 4 years (Vedeler et al., 2006). In our series, two cases with amphiphysin-IgG and anti-Yo respectively, were not detected with cancer during follow-up. These two antibodies are “well-characterized” paraneoplastic antibodies (Graus et al., 2004), so the patients were diagnosed as definite PNS according to the Graus criteria. Tumours were detected in 95% of patients with amphiphysin-IgG, and 98% with anti-Yo (Titulaer et al., 2011). It has been hypothesized that the failure to demonstrate cancer in such patients is because of efficient antitumour immune responses. However, it is likely that the increased use of highly sensitive imaging modalities, including FDG-PET, may detect indolent tumours.

Until now, the largest case series of paraneoplastic myelopathy reported included 31 patients (Flanagan et al., 2011c). The characteristic MRI finding is of longitudinally extensive, symmetric, tract-specific signal changes partly with gadolinium enhancement within the spinal cord. This pattern commonly involves the lateral columns, dorsal columns or central grey matter patterns, which was identical with the imaging finding in our cases (lateral column, 1; dorsal column, 1; central grey matter, 2). It should also be noted that the MRI may be

Table 1
Clinical characteristics of nine patients.

Patient NO.	Age, y/sex	presentation	Interval from onset to diagnosis, mo	Interval from onset to WC, mo	Interval from onset to last neurological evaluation, mo	Onconeural Ab	Neoplasm type	Interval between myelopathy and finding of cancer [a]	CSF count of White cells	CSF pro.	CSF specific OCB	MRI of spinal cord	Surgery/ chemotherapy/ Immunotherapy/ follow-up	Interval from onset to death
1	55/M	Subacute progressive myelopathy	1.5	3	22	CRMP-5 IgG	SCLC	1.5	38	188	+	C2-T12 spinal cord T2 signal abnormality, GM	+/−/−/D	24
2	46/F	Chronic progressive myelopathy	7	5	11	Ri	Breast ca.	7	16	39	+	T10–12 spinal cord T2 signal abnormality, GM	+/+/ Steroid /WC	
3	63/F	Chronic progressive myelopathy and stiff-person syndrome	40	18	56	Amphiphysin	−	−	3	55	+	T1–6 spinal cord T2 signal abnormality, tractopathy	−/−/Steroid/WC	
4	61/M	Chronic myelopathy and neuropathy	3	6	32	Hu	SCLC	15	0	138	+	−	+/−/−/WC	
5	49/M	Chronic myelopathy and neuroapthy	7	Wk	56	Hu	Colon ca	7	13	174	−	−	+/+/Steroid/Wk	
6	67 M	Chronic progressive myelopathy	19	10	19	−	Kidney ca	19	5	36	−	−	+/−/Steroid/WC	
7	60F	Chronic progressive myelopathy	7	2	20	NA	SCLC	-1	NA	NA	NA	−	+/−/−/D	23
8	64F	Subacute progressive myelopathy	1	9	13	Yo	−	−	102	28	+	T9–11 spinal cord T2 signal abnormality, tractopathy	−/−/− /WC	
9	71 M	Chronic progressive myelopathy	12	Wk	29	Hu	Lung cancer	12	4	60	+	−	−/+/ Steroid /Wk	

a, if cancer happens ahead, the interval will be negative. Abbreviations: Ab = antibody; ANNA = antineuronal nuclear antibody; C = cervical cord; Ca = carcinoma; CRMP-5 = collapsin response-mediator protein–5; D = dead; GM = grey matter; mo = month; NA = not available; pro = protein; SCLC = small-cell lung carcinoma; T = thoracic cord; WC = wheelchair; Wk = walker.

normal in up to half of cases. Tract-specific abnormalities on MRI may be seen in some metabolic myelopathies and nutritional deficiencies. Though the images in these disorders do not usually enhance with gadolinium, there was only one case in our series where the MRI showed a slight enhancement, it is important to test vitamin B12 and copper in these patients (Hemmer et al., 1998; Kumar et al., 2006). Dorsal column signal abnormalities have been reported in patients with leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) (Kassem et al., 2014). Lateral column signal abnormalities have been reported in patients with spinal xanthomatosis (Abe et al., 2016). Related metabolic examinations or gene tests may be necessary for some patients with chronic progressive courses and negative onconeural antibodies. Longitudinally extensive T2 signal abnormality in MRI can also be seen in some inflammatory disorders, such as neuromyelitis optica (NMO) and neurosarcoidosis. Ocassionally NMO can have subacute or chronic onset (Salazar et al., 2012). Hyperintensity on T2-weighted images in NMO is more heterogeneous and gadolinium enhancement is usually patchy when compared with that of parneoplastic myelopathy. All the cases in our study were AQP4-Ab negative. It should be noted that there is increasing evidence that cancer can be linked to some cases of NMOSD (Cai et al., 2016; Sepúlveda et al., 2017). In some paraneoplastic NMOSD cases, tumour tissue had been confirmed histologically expressing aquaporin-4 (Beauchemin et al., 2018). Spinal cord sarcoidosis (SCS) could present solely as subacute or chronic autoimmune myelopathy, which could have longitudinally extensive spinal cord lesions on an MRI. However SCS patients have constitutional symptoms and hilar adenopathy more frequently than NMOSD. Some SCS patients have CSF hypoglycorrhachia, elevated angiotensin-converting enzyme, which are exclusive to SCS (Flanagan et al., 2016), Besides, persistent dorsal cord subpial gadolinium enhancement over 2 months favored SCS (Zajicek et al., 1999).

The treatment of paraneoplastic myelopathies includes detection and treatment of the underlying cancer, immunotherapy for myelopathy in some patients. However, due to the probable CD8+ cytotoxic T cell destruction, most patients respond poorly to the treatment. On follow-up, only two patients remained stable in our case series. Both of them got chemotherapy, which usually has immunosuppressive effect and may benifit paraneoplastic myelopathy accordingly. In Fanagan et al.'s study, only 3 of 26 patients had sustained improvement on follow-up (Flanagan et al., 2011c). Due to the rarity of paraneplastic myelopathy, there is no evidence-based treatment. Improvements or stability have been reported based on case reports or case series with the following treatments alone or in combination: steroid (Leypoldt et al., 2006; Keegan et al., 2008; Rajabally et al., 2008; Flanagan et al., 2011c), cyclophosphamide (Keegan et al., 2008; Flanagan et al., 2011c), mycophenolate mofetil (Keegan et al., 2008; Flanagan et al., 2011c), azathioprine (Keegan et al., 2008; Flanagan et al., 2011c), rituximab (Frasquet et al., 2013), plasma exchange (Flanagan et al., 2011c), and oncologic treatment (Anderson and Borsaru, 2008; Flanagan et al., 2011c). Paraneoplastic myelopathy appears to be associated with significant morbidity and poor response to therapy.

5. Conclusion

Paraneoplastic myelopathy is a rare and progressive spinal cord disease. Most of patient CSF have inflammatory characteristics. Nearly half of the patients have symmetric, longitudinally extensive grey matter or tract-specific changes on their spinal cord. It is associated with significant morbidity and has a poor response to treatment.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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