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Paraneoplastic myeloneuropathies: Clinical, oncologic and serologic accompaniments

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Abstract

Objective: To test the hypothesis that myeloneuropathy is a presenting phenotype of paraneoplastic neurological syndromes, we retrospectively reviewed clinical, radiological and serological features of 32 patients with concomitant paraneoplastic spinal cord and peripheral nervous system involvements.

Methods: Observational study investigating patients with myeloneuropathy and underlying cancer and/or onconeural antibody seropositivity.

Results: Among 32 paraneoplastic myeloneuropathy patients, twenty (63%) were women with median age 61 years (range 27-84 years). Twenty-six patients (81%) had classified onconeural antibodies (amphiphysin, n=8; ANNA1 [anti-Hu] n=5; CRMP5 [anti-CV2], n=6; PCA1 [anti-Yo], n=1; PCA2, n=2; KLHL11, n=1; and combinations thereof: ANNA1/CRMP5, n=1; ANNA1/amphiphysin, n=1; ANNA3/CRMP5, n=1). Cancer was confirmed in twenty-five cases (onconeural antibodies, n=19; unclassified antibodies, n=3; no antibodies, n=3). Paraneoplastic myeloneuropathies had asymmetric paresthesias (84%), neuropathic pain (78%), subacute onset (72%) sensory ataxia (69%), bladder dysfunction (69%), and unintentional weight loss >15 pound (63%). Neurological examination demonstrated concomitant distal or asymmetric hyporeflexia and hyperreflexia (81%), impaired vibration and proprioception (69%), Babinski response (68%), and asymmetric weakness (66%). MRI showed longitudinally-extensive (45%), tract-specific spinal-cord T2-hyperintensities (39%) and lumbar nerve root enhancement (38%). Ten of twenty-eight (36%) were unable to ambulate independently at last follow-up (median: 24 months, range 5-133 months). Combined oncologic and immunologic therapy had more favorable modified Rankin scores at post-

treatment follow-up compared to those receiving either oncologic or immunologic therapy alone (2 [range 1 to 4] vs 4 [range 2 to 6] p<0.001).

Conclusions: Paraneoplastic etiologies should be considered in the evaluation of subacute myeloneuropathies. Recognition of key characteristics of paraneoplastic myeloneuropathy may facilitate in early tumor diagnosis and initiation of immunosuppressive treatment.

Introduction

Myeloneuropathies are defined by the concomitant development of peripheral nerve and spinal cord involvement.[1, 2] Etiologies usually associated with myeloneuropathy include metabolic (vitamin B12 or copper deficiency), inflammatory, infectious, hereditary or toxic. Paraneoplastic neurological syndrome Euronetwork diagnostic criteria (2004) included paraneoplastic encephalomyelitis, limbic encephalitis, cerebellar degeneration, subacute sensory neuronopathy, and chronic gastrointestinal pseudo-obstruction as "classical paraneoplastic phenotypes".[3] Paraneoplastic myelopathy and sensorimotor neuropathy were individually described as non-classical syndrome but paraneoplastic myeloneuropathy was not specifically described.

Myelopathy and neuropathy as manifestations of paraneoplastic disorders have been described in association with breast and lung cancers.[4, 5] These may occur in isolation or as part of a multi-focal neurological disorder, primarily due to immune targeting of intracellular neural antigens. The sequential development of myelopathy and neuropathy has been described in cases of breast adenocarcinoma or small cell lung cancer, particularly in association with amphiphysin-IgG, type 1 anti-neuronal nuclear antibody (ANNA-1, a.k.a. anti-Hu), but the concomitant development of neuropathy and myelopathy in paraneoplastic disorders remains largely limited.[6, 7] Case reports of myeloneuropathy in association with testicular cancer with anti-Ma2-IgG, and breast cancer have been reported.[8-11] Patients with underlying cancers have also been reported to develop nutritional-deficiency myeloneuropathies, posing a diagnostic dilemna.[12, 13] Therefore, recognition of characteristics which can help distinguish paraneoplastic etiologies may aid in earlier diagnosis and management.[14] Herein, we

describe a single-center cohort of patients with paraneoplastic myeloneuropathy, and review the associated diagnostic characteristics.

Methods

Standard Protocol Approvals, Registration and Patient Consents

The study was approved by the institutional review board of Mayo Clinic, Rochester, Minnesota (IRB#08-006647). Electronic medical records and neuroimmunology laboratory databases between 1995 and 2019 were used to identify patients developing clinically, radiographically, or with electrodiagnostic evidence of myelopathy and peripheral neuropathy. [15-17]

Patients with concomitant development of peripheral nerve, and/or root, and spinal cord involvement within a three-month timeframe with supportive evidence of multifocal involvement in both clinical and radiographic or electrodiagnostic domains were included. Cases with co-existing encephalopathy at onset or isolated motor neuron involvement were excluded.

Paraneoplastic association was defined by presence of onconeural autoantibody in the serum with >70% neoplastic association and/or a diagnosis of neoplasm within three years of symptom onset and exclusion of alternative causes such as multiple sclerosis (MS) or neuromyelitis-optica-spectrum-disorder.[3] Furthermore, patients with vitamin B12 or copper deficiency, human immunodeficiency virus infection, prominent neuropathy attributed to chemotherapy by historical documentation, and neoplastic infiltration of the CNS were excluded.

Search terms used to identify cases included: myeloneuropathy, paraneoplastic myelopathy, paraneoplastic neuropathy, paraneoplastic sensory neuronopathy,

paraneoplastic polyradiculoneuropathy, paraneoplastic motor neuron disease, and paraneoplastic encephalomyelitis. Laboratory databases by discrete onconeural antibody positivity (CRMP5, ANNA1, amphiphysin, PCA2) and cancers (breast adenocarcinoma, small cell lung cancer, testicular cancer) were also used to identify patient.[7, 18-23]

Medical records of patients that met the stated criteria were reviewed by three neurologists (S.S., R.D.C, D.D.) for demographic, clinical, electrophysiological and radiographic data. Outcomes were measured by ambulatory status and by change in modified Rankin score (mRS) before treatment and at last follow-up in those patients with available outcome data. A decrease in mRS scores of ≥1 was considered to be a favorable response.

Laboratory Methods

All patients were evaluated for onconeural antibodies to various specificities: ANNA1, ANNA2, ANNA3, CRMP5, anti-glial/neuronal nuclear antibody (AGNA1, or SOX1), Amphiphysin, Purkinje cell Cytoplasmic Antibody Type 1 (PCA1), Microtubule-associated protein 1B Antibody (MAP1B, a.k.a PCA2) and Kelch-like Protein 11 (KLHL11) in the Mayo Clinic Neuroimmunology Laboratory.[17-19, 22, 24, 25]

Indirect Immunofluorescence Assay for Antibody Detection

Patient serum were tested by indirect tissue based indirect immunoflousence on a cryosectioned (4 um) composite of adult mouse cerebellar, midbrain, cerebral cortex, hippocampus, kidney and gut tissue, as previously described.[19, 20] Samples with

characteristic staining patterns were titrated in doubling dilutions to determine the endpoint titer.

Recombinant protein western blot/ HEK293 Cells Overexpression Assay

Amphiphysin, MAP1B and CRMP5 antibody specificities was confirmed by Western blot analysis using recombinant human amphiphysin protein (full length), MAP1B fragment (amino acids 1-666) and CRMP5 (full-length), respectively.[15, 25] KLHL11 IgG detected on tissue immunofluorescence was confirmed by KLHL11 HEK293 overexpression cell based assay.[22, 26]

Statistical Analysis

Descriptive data was reporting using medians, ranges and percentages. Categorical and continuous variables were analyzed by Mann-Whitney U testing. The P value was two-sided and P values less than 0.05 were significant (JMP Pro 14).

Data Availability

All methods are available above and data are published in this article.

Results

Demographics, antibody and oncologic associations

Thirty-two patients had paraneoplastic myeloneuropathy as their initial presentation (**Table 1)**. Twenty were women (63%), and median age was 61 years (range 27-84 years). Chronic tobacco use was noted in 81% of patients (median 40 pack per year, n=26). Underlying malignancy was detected in 25 patients. Small cell lung cancer (n=11) and breast adenocarcinoma (n=7) were the most common malignancies, with further details shown in **Figure 1A-1C**. Neurologic symptoms manifested prior to

cancer diagnosis in 22/25 patients, and the remaining three cases had symptom onset within 3 years of cancer diagnosis.

Among 32 paraneoplastic myeloneuropathy patients, 20 had antibody evaluations in the serum and, 12 had both serum and CSF neural-specific antibody testing. Twenty-six had detectable onconeural antibodies: amphiphysin, n=8 (serum only, n=4; CSF and serum, n=4, median serum titer 1:3840, range 1:240-1:245760 [normal<1:120]; median CSF titer 1:64, range 1:4-1:960 [normal<1:4]); anti-neuronal-nuclear-antibody type-1 (ANNA1, anti-Hu), n=5 (serum only, n=4; CSF and serum, n=1, median serum titer 1:3840, range 1:240-1:122880; CSF titer 1:512); collapsing-response-mediator-protein-5 (CRMP5), n=6 (serum only, n=3; CSF and serum, n=3, median titer 1:3840, range 1:240-1:491520; median CSF titer 1:512, range 1:64-1:8192); purkinje-cell-cytoplasmic antibody type-1 (PCA1, anti-Yo), n=1(serum titer 1:240; CSF titer 1:16); PCA2 (microtubule-associated-protein-1B), n=2 (serum only, titers 1:240; 1:15360); kelch-like-protein-11(KLHL11), n=1 (serum titer 1:240 and CSF titer 1:4); and combinations thereof: ANNA1/CRMP5, n=1 (serum titer 1:960/1:240); ANNA1/amphiphysin, n=1 (serum titer 1:61440/1:30720; CSF titer 1:4/1:1024); ANNA3/CRMP5, n=1 (ANNA3 in serum titer 1:960, CRMP5 detected in both serum, titer 1:7680 and CSF titer 1:1024). Among these, nineteen were diagnosed with cancers. The remaining seven patients had imaging findings suggestive of neoplasm, but pathological confirmation was not available (**Figure 1B and 1C**). One patient had a breast mass, four had lung masses, and two had abdominal masses. Biopsy and histopathological analysis in two of these seven cases was non-diagnostic. In three patients, data regarding biopsy/histopathological evaluation of the mass was not present in the patient records.

In two patients, rapid neurologic deterioration and superimposed infection led to death prior to attempting biopsy. All six patients without characterized onconeural antibodies (unclassified neural specific antibodies, n=3 [two detected in serum, and one detected in both serum and CSF]) had pathologically confirmed cancer.

Clinical Characteristics

Patients frequently had a subacute presentation, defined as nadir of symptom severity occurring one to three months from onset (n=23, 72%). Two patients (6%) presented acutely within 1 month and seven (22%) presented with a more chronic decline. Most common clinical characteristics included: neuropathic pain (n=25, 78%), bladder dysfunction (n=22, 69%), asymmetric paresthesias (n=20, 63%), and unintentional weight loss of greater-than 15 pounds (n=20, 63%; median weight loss 20 pounds [range 15-75]). Neuropathic symptoms were non-length dependent (n=28, 88%) and radicular involvement was noted in 56% (n=18) of patients. Patients commonly had cramping, spasms or stiffness (n=17, 53%), and in two patients with amphiphysin autoantibodies, simultaneous peripheral nerve hyperexcitability. Orthostatic intolerance defined by clinical history of syncope or lightheadedness and blood pressure changes upon standing was seen in 14 patients (44%) with supportive autonomic reflex testing in 4 patients. Gastrointestinal dysmotility at onset, defined as new, severe post-prandial fullness or nausea, constipation, or diarrhea (n=14, 44%) was also common; one patient had gastric motility studies, which demonstrated prolonged colonic and small bowel emptying.

Neurological examination commonly demonstrated simultaneous hyporeflexia and hyperreflexia at different sites (n=26, 81%). Hyporeflexia was usually present distally or

in an asymmetric pattern. The majority of patients also had impaired vibration and proprioception (n=22, 69%), Babinski response (n=22, 68%), and asymmetric weakness (n=21, 66%). Weakness was noted in both upper and lower limbs in 44% of patients (n=14). 37% (n=12) of patients had isolated lower limb involvement and 19% (n=6) had isolated upper limb involvement.

Copper or vitamin B12 deficiency related subacute combined degeneration was the primary diagnostic consideration at disease onset in twenty-eight patients (88%) but was excluded by pertinent laboratory investigation. Among patients with CSF analysis (n=28), the majority (23, 82%) had inflammatory changes (median CSF cell count 8 cells/mm^3, range 0-74 cells/mm^3 [lymphocytic predominant] and median CSF protein 73 mg/dl, range 31-188 mg/dl). Four patients did not have CSF collected; two had normal spine MRIs, but both were positive for amphiphysin autoantibodies and had breast or small-cell lung cancer, respectively.

MRI Characteristics of Patients with Paraneoplastic Myeloneuropathy

Several notable imaging findings were observed, and representative images are provided in **Figure 2**. Imaging was not available for review in one patient. Spinal cord T2 hyperintensities were present in nineteen patients (61%), and fourteen (45%) were longitudinally extensive (≥3 vertebral segments) T2 lesions (**Table 1**). Twelve patients (39%) did not demonstrate any spinal cord MRI abnormalities, despite myelopathic findings on examination. T2 hyperintensities were tract-specific in twelve of the nineteen (63%) abnormal MRIs and were dorsal columns (n=6), lateral corticospinal tract (n=5) or both dorsal column and corticospinal tracts (n=1) (**Figure 2A-F**). Central gray matter abnormalities were also identified in nine patients (29%). Half of the tract-specific

lesions (n=6, 50%) had bilaterally symmetric involvement of the spinal cord tracts. Approximately one-third of patients (n=11, 35%) demonstrated active contrast extravasation. Ten patients (32%) demonstrated nerve root contrast enhancement, 8 limited to the lumbar roots **(Figure 2 G,H**).

Neuropathy Characteristics

Electrodiagnostic studies were performed in thirty-one patients, and all had electrophysiologic features suggestive of an axonal neuropathy. One patient additionally had some features of demyelination on nerve conduction studies, presumed secondary to axonal loss. One patient with clinically evident neuropathy did not undergo electrodiagnostic study. Clinical description of neuropathic pain radiating down one or more dermatomal distributions with proximal muscle weakness or evidence of denervation in the paraspinal muscles was considered indicative of radicular involvement. Polyradiculoneuropathy with evidence of nerve root and peripheral nerve involvement was the most common neuropathy phenotype (n=16, 50%), closely followed by distal, asymmetric sensorimotor neuropathy (n=10, 31%). Sensory ganglionopathy and symmetric length-dependent sensorimotor neuropathies were present in two and four patients, respectively.

Somatosensory evoked potentials performed in two patients demonstrated impairment in both central and peripheral proprioceptive pathway. Autonomic reflex testing was performed in 4 patients. Two patients had moderate-severe cardiovagal, adrenergic and post-ganglionic sudomotor dysfunction. One had adrenergic and postganglionic sudomotor dysfunction, and another had moderate-severe cardiovagal and adrenergic

impairments with preserved postganglionic sudomotor function, suggesting a limited autonomic failure.

Management and clinical outcomes

Ten patients received only immunotherapy, three received only oncologic therapy, and sixteen received both. Utilized first-line immunotherapies included one or more of the following: high-dose intravenous methylprednisolone (n=19), intravenous immunoglobulin (n=12), oral prednisone (n=12) or plasmapheresis (n=4). Additionally, a subset of these patients received long-term immunosuppression: cyclophosphamide (n=9), rituximab (n=2), mycophenolate mofetil (n=2) and azathioprine (n=2). Three seropositive patients without pathological diagnosis of neoplasm did not receive oncologic or immunologic therapy.

Median duration of follow-up was 24 months (ranging 5-133 months). Fifteen of 28 patients (53%) with long-term follow-up (>1 year follow up) had favorable clinical outcomes with cancer treatment and/or immunotherapy at subsequent follow-up. Another six patients stabilized, whereas seven continued to deteriorate despite therapy. At last known follow-up, 7 patients (22%) had died. Median follow-up for patients without identified malignancies was 11 months (range 10-20).

In patients receiving combination of oncologic and immunologic therapy, outcomes were significantly favorable (median mRS change at follow-up before and after treatment) in comparison to those receiving either oncologic or immunologic therapy alone (-2 [range -3 to 0] vs 0 [range -1 to 2], $p<0.001$). Furthermore, median mRS at post-treatment follow-up among the patients receiving combination therapy was significantly lower than

patients receiving either oncologic or immunologic therapy alone (2 [range 1 to 4] vs 4 [range 2 to 6] p<0.001).

Discussion

Paraneoplastic myeloneuropathies exist as their own unique clinical phenotype and may be a diagnostic consideration in the evaluation of myeloneuropathies. Key presenting features of paraneoplastic myeloneuropathy are subacute asymmetric weakness and paresthesias, severe neuropathic pain, sensory ataxia, bladder dysfunction and orthostatic intolerance. Examination reveals concomitant hyporeflexia and hyperreflexia, Babinski response, asymmetric weakness and numbness, and impaired vibration and proprioception. Diagnostic work up was remarkable for longitudinally-extensive, tract-specific T2-hyperintense spinal cord lesions, spinal cord or nerve root gadolinium enhancement and inflammatory cerebrospinal fluid. In this study wheelchair dependence at disease nadir among paraneoplastic myeloneuropathy patients was noted in a little more than half of the patients.

Gastrointestinal dysmotility and orthostatic intolerance seen in several patients was similar to previously reported paraneoplastic neuropathy studies. [15, 18] This may be primarily due to post-ganglionic autonomic nerve dysfunction, as suggested by the quantitative sudomotor axon reflex changes noted among all patients who underwent autonomic reflex screen. However, dysfunction of sympathetic and/or parasympathetic pre-ganglionic neuronal tracts within the spinal cord may also have some contribution.[4, 27]

Some of these distinguishing characteristics, especially including sensory ataxia, have been highlighted in prior case reports of paraneoplastic myeloneuropathies.[8, 9 11]

Longitudinally extensive tract-specific changes on MRI have been similarly reported in a seronegative paraneoplastic myeloneuropathy patient associated with breast cancer.[8] Autoimmune myeloneuropathies without a strong oncological association have also been described among patients with adaptor-protein-3B2 autoimmunity and Sjogren's syndrome.[28, 29]

In our study, small cell lung cancer and breast adenocarcinoma were the most common oncological associations (53%), similar to prior reports of paraneoplastic myelopathies or neuropathies.[4, 17 30] The majority of cancers were detected at an early stage (n=18, 72%), supportive of either a potent anti-cancer immune response or indicative of earlier cancer detection due to paraneoplastic neurological manifestations. ANNA1, CRMP5 and amphiphysin were the most common autoantibody specificities noted (**Figure 1**). Intracellular localization of the autoantigens for the majority of these antibodies supports the significant role of autoantigen specific T-cell response among these cases.[31] These findings demonstrate that paraneoplastic myeloneuropathy presentation, similar to other classic or non-classic paraneoplastic phenotypes, can be seen in association with various onconeural antibodies and cancer.[3]

Comprehensive neuropathological analysis of well-characterized paraneoplastic myeloneuropathy is lacking. However, histopathological assessment of spinal cord and nerve biopsies of patients presenting with paraneoplastic myelopathy or neuropathy demonstrates perivascular cuffing of CD8+ T lymphocytes, supporting a cytotoxic T-cell mediated pathogenesis.[18, 32] Concern may exist regarding immunosuppression reducing anti-cancer response or potential drug interactions with other cancer chemotherapies; however, the majority of myeloneuropathy patients who received early, combined

cancer and immunosuppressive therapy had favorable long-term clinical outcomes.[33] This dual approach of removal of antigen source and immune response suppression has been successfully utilized in classical PNS.[34]

Paraneoplastic myeloneuropathy phenotype differs from paraneoplastic motor neuron disease, due to predominance of sensory involvement.[35] Due to lack of encephalitis among these cases, the term "encephalomyelitis" does not provide accurate information about the neurological localization of this paraneoplastic phenotype.[3] Longitudinally extensive tract specific MRI findings (**Figure 2**), are common among paraneoplastic myeloneuropathies, which have also been described in isolated paraneoplastic myelopathies as well.[4, 24] These radiographic features are distinct from demyelinating diseases such as multiple sclerosis, which are characterized by shorter segment, frequently asymmetric, unilateral lesions.[36, 37] Copper deficiency can present with myeloneuropathy with symmetric dorsal column abnormalities on imaging, but can be distinguished by its chronic disease course and lack of associated neuropathic pain.[38, 39] Other notable radiographic findings such as central gray matter involvement and gadolinium enhancement of the intramedullary spinal cord and nerve roots can also help distinguish this syndrome from metabolic myeloneuropathies. It is also important to note that few patients with paraneoplastic myeloneuropathy did not have imaging abnormalities but nevertheless had other supportive clinical and paraclinical findings consistent with myeloneuropathy. Among these, all patients who underwent CSF analysis had inflammatory changes supportive of immune-mediated pathogenesis. This is a retrospective study and some cases had limited long-term follow-up data. Limitations of this approach include the potential to overlook this entity if clinical

diagnosis or identifiable terminology was not included in clinical documentation, particularly patients in whom diagnostic evaluations were performed between several institutions. No minimum follow-up was required for inclusion of patients. Longer follow-up and repeated cancer screenings may have provided more definitive evidence of neoplasm and highlights the importance of the guideline driven approach to repeat testing at 6-12 month intervals for two years when suspecting paraneoplastic neurological syndrome.[3, 40, 41]

The observations from our study may provide insights into this rare yet distinguishable paraneoplastic phenotype.[14] Recognition of described subacute sensory predominant phenotype of concomitant myelopathy and neuropathy may aid in differentiation from other causes of myeloneuropathy, early cancer diagnosis and potentially favorable neurologic outcomes with combined oncologic and immunosuppressive therapy.

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Appendix 1: Authors

Name	Location	Contributions
Shailee Shah, MD	Mayo Clinic	Acquired the data; analyzed the data; interpreted the data; drafted the manuscript; revised the manuscript for intellectual content.
Rocio Do Campo Vazquez, MD	Mayo Clinic	Acquired the data; interpreted the data; revised the manuscript for intellectual content
Sean J Pittock MD	Mayo Clinic	Interpreted the data; revised the manuscript for intellectual content
Andrew McKeon MD	Mayo Clinic	Interpreted the data; revised the manuscript for intellectual content
Neeraj Kumar, MD	Mayo Clinic	Interpreted the data; revised the manuscript for intellectual content
Eoin Flanagan	Mayo Clinic	Interpreted the data; revised the manuscript for intellectual content
Christopher J Klein MD	Mayo Clinic	Interpreted the data; revised the manuscript for intellectual content
Divyanshu Dubey, MD	Mayo Clinic	Design and conceptualized study; analyzed the data; drafted the manuscript; revised the manuscript for intellectual content; study supervision

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Table 1: Clinical characteristics, diagnostic studies and outcomes of paraneoplastic myeloneuropathies.

Clinical Characteristics	**No. /Total No. (%)**
Age at onset, year (range)	61 (27-84)
Female	20/32 (63)
Subacute onset	23/32 (72)
Neuropathic pain	25/32 (78)
Sensory ataxia	22/32 (69)
Asymmetric sensory abnormalities	22/32 (69)
Loss vibration and proprioception	22/32 (69)
Bladder dysfunction	22/32 (69)
Babinski response	22/32 (68)
Asymmetric weakness	21/32 (66)
Unintentional weight loss	20/32 (63)
Orthostastic intolerance	14/32 (44)
GI dysmotility	14/32 (44)
Malignancies identified (pathologically confirmed)	25/32 (78)
MRI characteristics	
Intramedullary T2 hyper-intensities involving MRI spine	19/31 (61)
Longitudinally extensive T2 lesion (>3 vertebral segments)	14/31 (45)
Tract specific T2 hyper-intensities	12/31 (39)
Lumbar root enhancement	8/21 (38)
Intramedullary spinal cord enhancement	11/31 (35)
Gray matter involvement	9/31 (29)
CSF Characteristics	
Elevated CSF protein, >50 mg/dL	22/28 (79)
CSF elevated white blood cell count, >5 cells/uL	17/29 (59)
Supernumerary CSF oligoclonal bands	11/21 (52)
Clinical outcomes	
Wheelchair dependent at attack nadir	20/32 (63)
Clinical improvement	15/28 (54)
Wheelchair bound at last follow-up	10/28 (36)
Duration of follow-up, median (range), months	24 (5-133)

Key: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

Figure legends
Figure 1: Cancer and onconeural antibody associations.

Summary of onconeural antibodies and presence of cancer (A), three patients had unclassified neural specific antibodies. Cancer association in 25 patients (B). Among 7 patients no neoplasms were identified.

Key: ANNA1, anti-neuronal nuclear-antibody type1 (a.k.a. anti-Hu); ANNA3, anti-neuronal nuclear-antibody type 3; CRMP5, Collapsing Response Mediator Protein 5 (a.k.a. CV2) ; PCA1, Purkinje cell Cytoplasmic Antibody Type 1; KLHL11, Kelch-like Protein 11

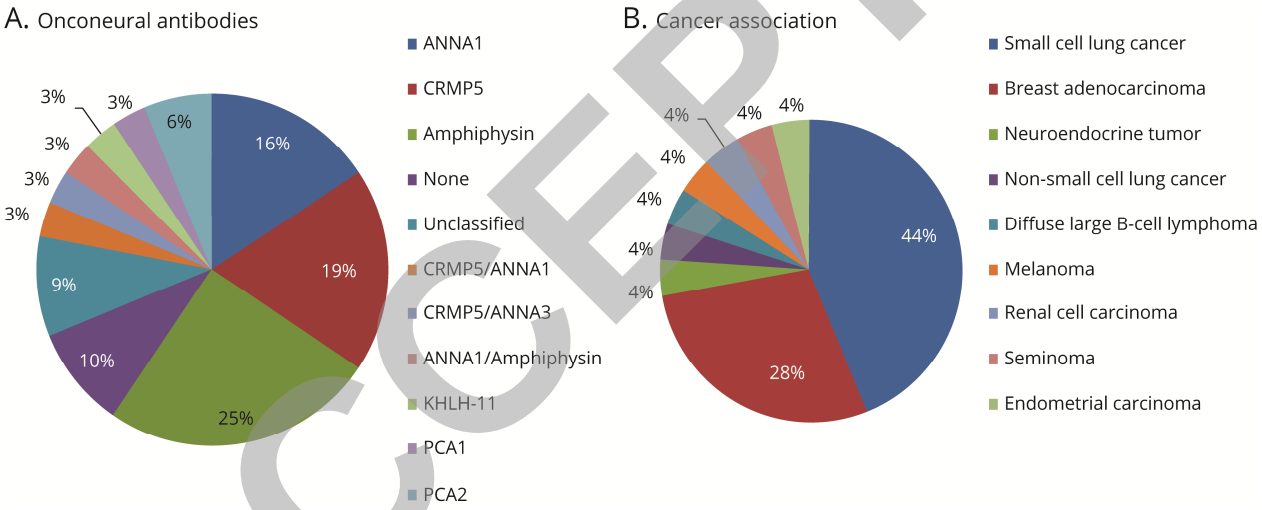
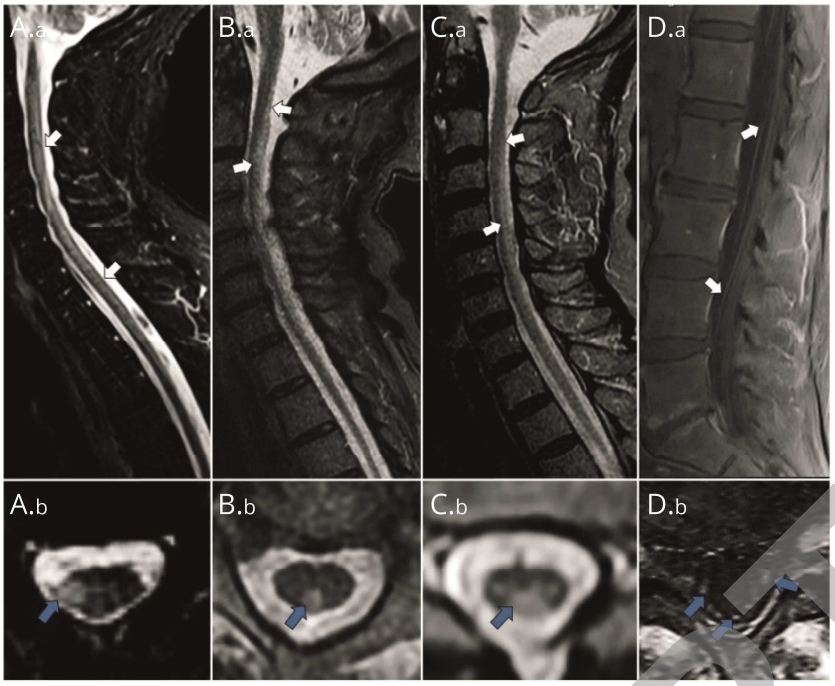


Figure 2: MRI spine abnormalities in paraneoplastic myeloneuropathies.

Cervical, thoracic and lumbar spine MRI sagittal (A.a, B.a, C.a, D.a) and axial (A.b, B.b, C.b, D.b) sequences. (A.a, A.b) CRMP5 IgG seropositive adult patient with asymmetric, longitudinally extensive T2-hyperintense lesion (white arrow) involving the right corticospinal tracts (blue arrow) with a concomitant axonal polyradiculoneuropathy. (B.a, B.b) ANNA1 and amphiphysin IgG seropositive adult patient with longitudinally extensive T2-hyperintense lesion (white arrow) right dorsal column (blue arrow) with a concomitant sensory neuronopathy. (C.a, C.b) ANNA1 IgG seropositive adult patient with symmetric, bilateral, longitudinally-extensive T2-hyperintense lesion (white arrow) involving the dorsal columns (blue arrows) and concomitant sensory predominant length dependent axonal polyneuropathy (D.a, D.b). Adult patient with unclassified neural specific antibody with diffuse nerve roots enhancement on post-gadolinium T1 weighted sagittal (white arrow) and axial (blue arrow) sequences with a concomitant axonal polyradiculoneuropathy.

Key: ANNA1, anti-neuronal nuclear-antibody type1 (a.k.a. anti-Hu); CRMP5, Collapsing Response Mediator Protein 5 (a.k.a. CV2)



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