Successful immunosuppressive treatment and long-term follow-up of anti-Ri-associated paraneoplastic myelitis

Antineuronal antibody-associated paraneoplastic neurological syndromes (PaNSs) result from tumour-stimulated autoimmune attacks against components of the nervous system. The rare antineuronal antibody anti-Ri (ANNA-2) was initially thought to be closely associated with paraneoplastic opsoclonus–myoclonus syndrome. Recently, however, it has been found in several other PaNSs.[1] First-line treatment in PaNSs is removal of the underlying tumour. Second-line treatment is immunosuppression, which, although extensively used, especially when no tumour is detected, is often ineffective. Often, patients die from relentlessly progressive PaNS rather than the underlying neoplasm.[2] Here, we report the 2-year follow-up of an anti-Ri-positive steroid-responsive myeloneuropathy. No tumour was detected. Immunosuppressive treatment was tailored on the basis of clinical relapses, inflammatory changes in cerebrospinal fluid (CSF) and somatosensory evoked potentials (SEPs).

A 65-year-old woman, a retired administrator, was referred to our department with a 10-month history of progressive gait difficulties and ascending sensory loss in her legs, eventually having become wheelchair bound. Her medical history was unremarkable apart from enlarged axillary lymph nodes that were excised 9 months earlier. Histological examination showed only inflammatory changes. She had received hormone replacement therapy for 11 years. She never smoked.

On neurological examination, deep tendon reflexes were absent. She had spastic paraparesis with bilateral extensor plantar responses. Bilateral hypaesthesia for light touch up to the knees and diminished vibration sense were observed distally in her legs. Magnetic resonance imaging (MRI) showed symmetrical T2-hyperintense multisegmental (C6–TH3/TH8–TH12) cervicothoracal lesions of the spinal cord, with gadolinium enhancement restricted to the lateral parts (fig 1A). Cerebral MRI showed only minor microangiopathic changes. Nerve conduction studies showed normal tibial nerve conduction velocities (NCV), slightly reduced right median NCV (forearm 41 m/s, normal >41 m/s) and moderately reduced sural NCV (32 m/s, normal >40 m/s). Right median (32 ms, normal 28 ms) and tibial (61 ms, normal 52 ms) nerve F-wave latencies were prolonged, in keeping with polyneuropathy. SEPs after median nerve stimulation were normal; tibial SEP was absent bilaterally. An examination of the CSF showed pleocytosis (80% lymphocytes) and disturbed blood–CSF barrier (fig 1B). Microbiological serology of serum and CSF showed no evidence of acute infection. Routine laboratory tests were normal. Rheumatoid factor, anti-neutrophil and anti-nuclear autoantibodies were not found. Immunofluorescence screening for onconeural antibodies using monkey cerebellum, jejunum and peripheral nerve showed high-titre antineuronal nuclear antibodies in serum (1:1920) and CSF, with a pattern suggestive of anti-Ri antibodies. Subsequent immunoblots with recombinant targets of anti-Ri, anti-Hu, anti-Yo and amphiphysin antibodies (serum or CSF) confirmed anti-Ri specificity. In addition, no anti-Ma2, anti-CRMP5, anti-ANNA-3, anti-PCA2, anti-PCA-Tr, anti-N or anti-P/Q-calcium channel, anti-striated muscle or anti-acetylcholine receptor antibodies were found. Whole-body fluordeoxyglucose-positron emission tomography (FDG-PET) was inconspicuous. Mammography showed bilateral mastopathy. Carcinoembryonic antigen, CA15-3, CA125, α-fetoprotein, human chorionic gonadotropin, and β2-microglobulin were not raised.

The patient was treated with high-dose steroids for 14 days. In weeks, she regained the ability of walking with support. Sensory disturbances improved. Plantar responses became flexor. A first relapse (relapse 1, fig 1B) led to a recurring inability to walk unaided, reappearance of extensor plantar responses and sensory deficits for all qualities below TH12. Spinal MRI showed increased signal abnormalities and gadolinium enhancement. The number of white blood cells in the CSF increased and blood–CSF barrier dysfunction became pronounced. Although a high-dose steroid treatment and slow tapering led to improved muscle strength, reduced sensory disturbances and increased walking distance as well as normalisation of abnormalities of the CSF, in the ensuing year, two more relapses (fig 1B) were witnessed, each after tapering steroids below 20 mg prednisolone and associated with the reappearance of inflammatory CSF (fig 1B). Increased prednisolone was followed by clinical improvement and alleviated abnormalities of the CSF. Peroneal SEP latencies were established as an additional parameter. Every relapse led to increased residual deficits. Eventually, oligoclonal bands appeared and remained detectable, mild pleocytosis persisted and peroneal SEP continued to deteriorate. As steroidal side effects were no longer tolerable, monthly cyclophosphamide-pulsed treatment (650 mg/m^2 body surface) was started. During the following 9 months, the patient's condition stabilised and CSF findings normalised. Six-monthly FDG-PET did not disclose an underlying malignancy. Owing to side effects, cyclophosphamide was eventually discontinued. As azathioprine and mycophenolate mofetil led to lymphopenia, intravenous immunoglobulins were started recently. So far, there has been no relapse.

This patient with anti-Ri antibodies presented with myeloneuropathy. The non-classical clinical presentation in combination with a well-characterised onconeural antibody fulfils the criteria of a definite PaNS.[3] That no tumour was detected during 36 months is compatible with anti-Ri PaNS. Only 3% of patients have not developed cancer within 3 years of follow-up.[1 3] The history of enlarged lymph nodes, oestrogen treatment and mastopathy is suggestive of

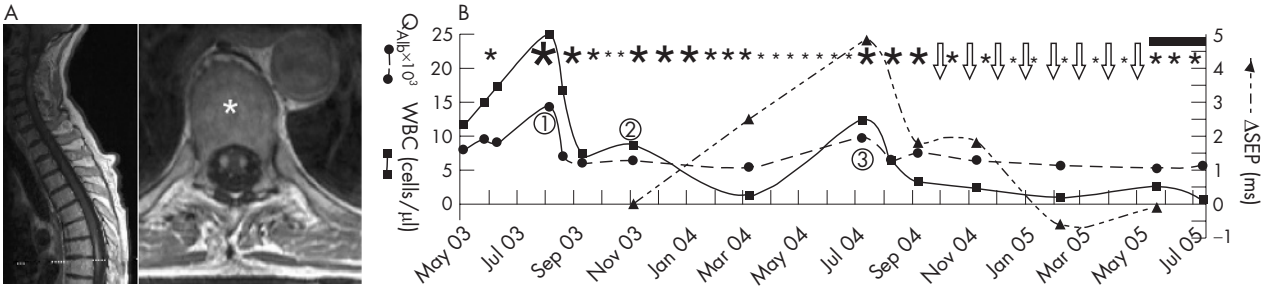

Figure 1 (A) Coronal and sagittal sections of gadolinium-enhanced T1-weighted spinal magnetic resonance image showing symmetrical contrast enhancement of the lateral aspects of the spinal cord. Asterisk indicates TH12. Dashed line indicates the level of axial section. (B) Clinical course of the patient starting from May 2003. Continuous line with closed boxes: white blood cells (WBCs (cells/µl), left y axis, normal <5/µl) in the cerebrospinal fluid; dashed line with filled circles: $Q_{Alb}\times10^3$ (albumin ratio serum/cerebral spinal fluid as a parameter of blood brain–barrier function, left y axis, normal <8.4); dashed line with filled triangles: differences of left peroneal somatosensory evoked potential (SEP) latencies compared with those from November 2003 (ms, right y axis). Encircled numbers: numbered clinical relapses; open arrows: cyclophosphamide pulses; line of asterisks: steroid treatment, roughly corresponding in size of dose; filled line above asterisks: azathioprine treatment.

occult breast cancer; however, histological examination and PET scanning remained negative. Another autoimmune non-paraneoplastic aetiology of myelitis cannot be excluded completely. However, no other autoantibodies—for example, rheumatoid factor and Sjogren's syndrome antibodies—and no systemic manifestations were detected. Immunofluorescence and recombinant immunoblot confirmed anti-Ri specificity; however, no immunoblot using cerebellar extracts was carried out. Therefore, antibodies targeting neuronal proteins other than those tested cannot be excluded.

Classically, anti-Ri antibodies occur in PaNS with brain stem dysfunction.[1 4 5] Spinal involvement has been described in 12–16% of cases,[1 4 5] but, to our knowledge, this is the first detailed clinical and MRI description of anti-Ri myelitis with distinct signal abnormalities not usually encountered in infectious or other autoimmune myelitis. Although polyneuropathy was previously reported in 20% of anti-Ri patients, in almost half of these cases, additional onconeural antibodies (anti-Hu, CRMP5/CV2) were also present.[1] As none of these were detected in this case, it is plausible that myeloneuropathy was directly related to anti-Ri antibodies.

The long-term treatment of patients with PaNS without detectable cancer is a challenging situation. It is often unclear whether clinical improvements can be attributed to treatment or simply reflect the natural clinical course. In the present case, the former seems more likely. Over 2 years, both starting and increasing the dosage of steroids was followed by clinical improvement and reduced CSF inflammatory changes. As a corollary, tapering of steroids had an opposite effect. Of note, steroid responsiveness was previously reported also in patients with other anti-Ri positive PANSs.[1 4 5]

In summary, we report a patient with anti-Ri positive myeloneuropathy responding to immunosuppression. White blood cells in the CSF, CSF–blood-barrier function and peroneal SEPs proved to be useful in monitoring therapeutic responses. This case shows that long-term treatment of anti-Ri PaNS can be successful, but still remains a challenge.

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