

Severe parkinsonism
associated with anti-CRMP5
antibody-positive
paraneoplastic neurological
syndrome and abnormal
signal intensity in the bilateral
basal ganglia

INTRODUCTION

Anticollapsin response mediator protein 5 antibody (anti-CRMP5 antibody, also known as anti-CV2 antibody) is usually

associated with small-cell lung carcinoma (SCLC) or thymoma.¹ Although optic neuropathy, cerebellar ataxia and chorea are considered typical clinical features of paraneoplastic neurological syndrome (PNS) associated with anti-CRMP5 antibody, the neurological involvement of anti-CRMP5 antibody is broader.¹ We report the first known case with anti-CRMP5 antibody-associated PNS presenting with predominant parkinsonism and bilateral signal abnormalities in the caudate and putamen on brain MRI.

CASE REPORT

A 72-year-old man presented with a 6-month history of ambulatory disturbance. After the patient noticed sialorrhoea in September 2010, he began to develop a stooped posture, and short-stepped and propulsive gait. In January 2011, he noted gradual onset of dysarthria and constipation. His gait instability became severe, and by April 2011, he was only able to walk with assistance. He reported to our hospital in May 2011. On neurological examination, he was alert and communicative. His speech consisted of a low monotonous voice. Although he had marked bradykinesia and exhibited facial masking, no rigidity or tremor was observed. He shuffled when he walked with assistance, had a stooped posture and his arm swing was decreased bilaterally. Severe postural impairment was noted on the pulling test. Brain MRI showed bilateral lesions in the lenticular and caudate nuclei, which were hyperintense on T2-weighted images and fluid-attenuated inversion recovery images, and hypointense on T1-weighted images (figure 1A–C).

The differential diagnoses included infective pathology such as HIV and Japanese encephalitis virus, inflammatory demyelination, genetic metabolic causes, intoxication and neurodegeneration. The following tests were normal or negative: full blood count, C reactive protein, liver and renal function tests, HIV1 and 2 tests, syphilis serology, copper studies and anti-nuclear antibody tests. A serum study showed high concentrations of progastrin releasing peptide and neuron-specific enolase (413 and 46.4 ng/mL, respectively), and a truncal CT scan revealed a small lung nodule and swollen lymph nodes in the mediastinum (figure 1G, H). The patient underwent a lymph node biopsy, and the pathology was compatible with SCLC (figure 1I, J). Serum and cerebrospinal fluid studies showed a high titre of anti-CRMP5 antibodies; cerebrospinal fluid examination was otherwise unremarkable. Other paraneoplastic markers including anti-Hu antibody, anti-Yo antibody,

anti-Ri antibody, anti-Tr antibody, anti-Ma2 antibody and anti-amphiphysin antibody were negative. Based on the recommended diagnostic criteria for PNS, we diagnosed this patient as definite PNS with non-classical symptoms, SCLC, and positive for an onconeural antibody.²

Three courses of chemotherapy with etoposide and carboplatin were performed followed by radiation therapy, producing partial tumour shrinkage (figure 1K, L). This therapy also partially reduced the abnormal signal intensity on the brain MRI (figure 1D–F). Although L-dihydroxyphenylalanine (L-DOPA) treatment (300 mg/day) did not alleviate the patient's gait freezing, he became ambulatory with assistance after the chemoradiation therapy. During the follow-up period of 4 years and 1 month, he has shown no recurrence of severe parkinsonism.

DISCUSSION

PNS is a heterogeneous group of neurological disorders caused by mechanisms other than tumour metastases, metabolic and nutritional deficits, infections, coagulopathy or side effects of cancer treatment. This syndrome may affect any part of the nervous system from the cerebral cortex to neuromuscular junctions and muscles, and may damage one area such as Purkinje cells or presynaptic cholinergic synapses, or multiple areas presenting as encephalomyelitis. Although the pathogenesis of PNS is incompletely understood, immunological factors are believed to be important because autoantibodies and T-cell responses against nervous system antigens have been described for PNS.

Golbe *et al*³ reported the first case of paraneoplastic parkinsonism with metastatic carcinoma of the breast in a patient who rapidly developed parkinsonian signs and symptoms. Similar to our case, this patient did not respond to typical Parkinson's disease medications (ie, L-DOPA). No autoantibodies were found in the serum of the patient described by Golbe *et al*, and the patient ultimately succumbed despite chemotherapy. Other groups reported several cases of autoantibody-mediated parkinsonism, including cases positive for anti-Ri⁴ and voltage-gated potassium channel⁵ antibodies.

To our knowledge, this is the first documented case of anti-CRMP5 antibody-positive PNS characterised by severe parkinsonism and bilateral signal abnormalities in the basal ganglia on brain MRI. Some reports have described anti-CRMP5 antibody-positive patients who presented with parkinsonism in whom the underlying mechanisms were unclear.¹ In our case,

brain MRI suggests that parkinsonism associated with anti-CRMP5 antibodies may be caused by basal ganglia dysfunction. In support of this hypothesis, several cases have been reported of patients with anti-CRMP5 antibody-positive PNS who presented with chorea associated with signal abnormalities in the basal ganglia.⁶ As CRMP5 has not been reported to be expressed on the surface of basal ganglia cells,⁷ we do not know the exact reason why our patient exhibited bilateral abnormal intensity in the basal ganglia on brain MRI.

We have not administered any kind of immunomodulatory therapies to this patient because no strong evidence exists to indicate starting immunomodulation therapy for the treatment of PNS, and also because the best way to stabilise PNS is to treat the cancer as soon as possible.^{8–9} Indeed, PNS patients who have antibodies against cytoplasmic neuronal antigens such as CRMP5 do not improve with immunomodulation therapy.^{9–10} Furthermore, we were concerned that simultaneous use of immunosuppressive therapies and oncological treatments may result in increased toxicity.⁹ In our case, before starting chemoradiation therapy against SCLC, we treated the patient with L-DOPA to mitigate his parkinsonism, but no obvious effect was observed. We speculate that the reason for this failure is that basal ganglia postsynaptic neurons, which express dopamine receptors on the surface, are probably impaired by T cell-mediated cytotoxicity.¹⁰ This speculation is consistent with the findings of brain MRI in our patient.

In summary, we describe the first case presenting with severe parkinsonism associated with anti-CRMP5 antibody positivity and bilateral abnormal intensity in the basal ganglia on brain MRI.

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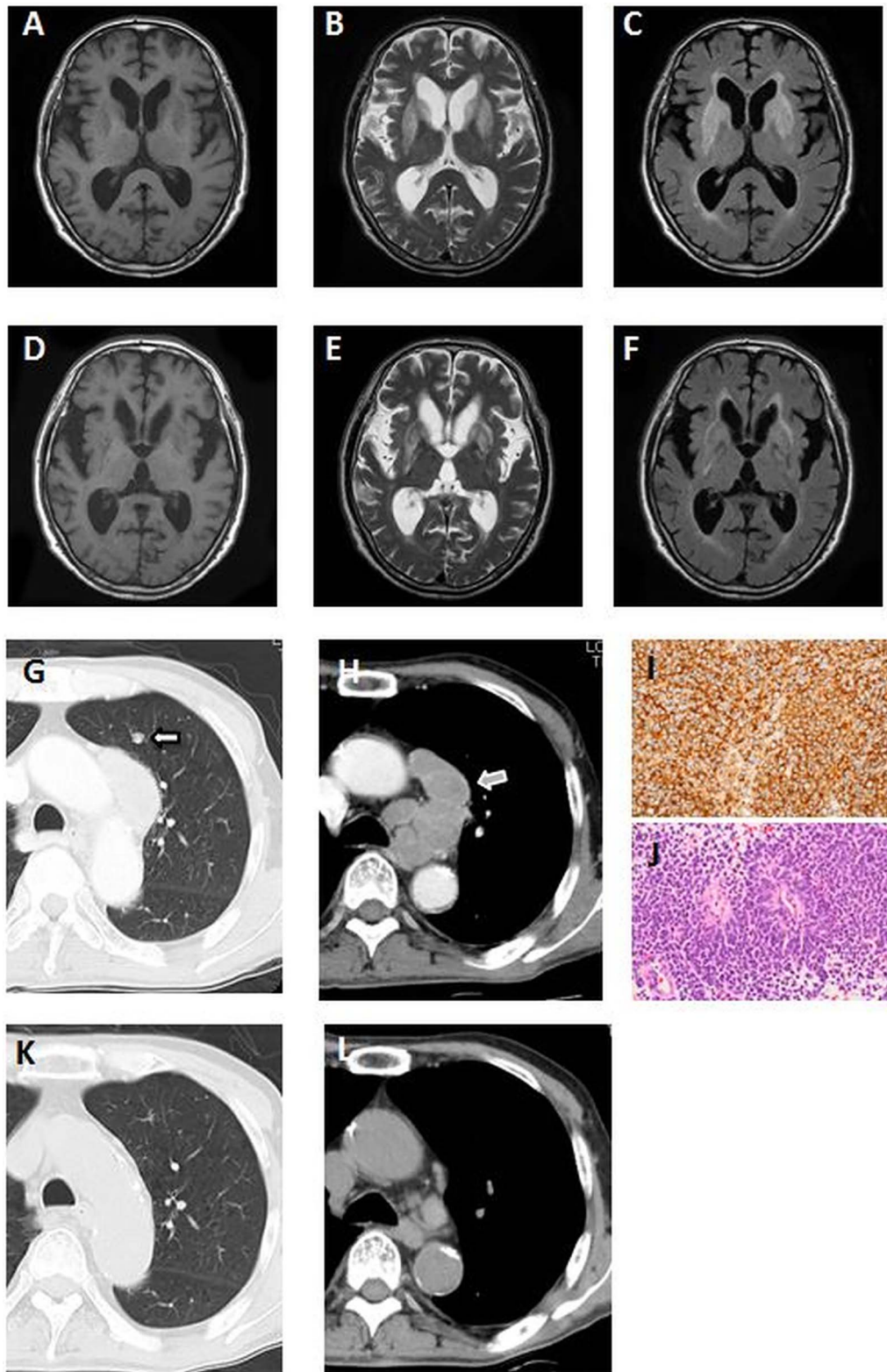


Figure 1 Axial T1-weighted, T2-weighted and fluid-attenuated inversion recovery image of the brain demonstrated symmetrical abnormal intensity of the putamen and caudate nuclei (A–C). Chemotherapy and radiotherapy aimed at treating the small-cell lung carcinoma (SCLC) partially ameliorated the abnormal signal intensity on the brain MRI (D–F). Lung CT with contrast injection revealed a nodule in the left anterior part of the lung (white arrow) (G) and swollen lymph nodes in the mediastinum (grey arrow) (H). The tumour was a SCLC. (I) Immunohistochemical analysis of the lymph nodes in the mediastinum with anti-CD56 antibodies and (J) H&E staining. Chemotherapy and radiotherapy produced a partial response in the nodule (K) and the lymph nodes (L). Original magnification of I and J, $\times 100$.

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