SHORT REPORT

Anti-Ma2 associated paraneoplastic neurological syndrome presenting as encephalitis and progressive muscular atrophy

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A 36 year old man with a history of testicular germ cell tumour presented six months after bilateral orchidectomy with progressive amnesia, irritability, vertical gaze palsy, and generalised seizures. Eight months after initial onset of symptoms, he demonstrated a head drop with muscular atrophy of the upper limbs, shoulder girdle, and posterior neck. He reported no sensory disturbances and his sensory examination was normal. The overall clinical presentation was consistent with motor neurone disease. Cerebrospinal fluid analysis revealed mild pleocytosis and increased protein concentration. Serum and cerebrospinal fluid were positive for the anti-Ma2 antibody by western blot analysis and immunostaining. Abnormal high signal in the grey matter was noted in the cervical spinal cord and brain by T2 weighted magnetic resonance imaging (MRI). The patient was treated with corticosteroids, intravenous immunoglobulin, and antiepileptic medication. The patient improved clinically and symptom progression ceased after initiation of treatment. There was complete resolution of the abnormal brain MRI lesions; however, the cervical spinal cord MRI lesion and muscular atrophy remained unchanged. It is suggested that the anti-Ma2 antibody is involved not only in encephalitis, but may also play a role in the cervical spinal cord lesions resulting in a motor neurone disease-like presentation.

Paraneoplastic neurological syndromes including paraneoplastic limbic encephalitis are neurological disorders that occur in patients with cancer.^{1–6} Paraneoplastic limbic encephalitis is often associated with small cell lung carcinoma and testicular germ cell tumours.^{1–6}

Recently, it was suggested that anti-Ma2 associated encephalitis differs from classic paraneoplastic limbic encephalitis because of its variable clinical features.⁶

Here, we report the clinical and neuroradiological findings in a patient with an anti-Ma2 associated paraneoplastic neurological syndrome who presented with encephalitis and progressive muscular atrophy.

To our knowledge, this is the first report describing the unique clinical features of a cervical spinal cord lesion confirmed by magnetic resonance imaging (MRI) in a patient with anti-Ma2 associated paraneoplastic neurological syndrome.

CASE REPORT

A 36 year old man was admitted to our hospital for progressive amnesia, hypersomnia, diplopia, and generalised convulsions in September 2003.

He had undergone a bilateral orchidectomy for testicular germ cell tumour six months before presentation. There was no recurrence of the tumour noted at the time of presentation.

On admission, the patient presented with confusion and seizures. There was no cerebellar ataxia or sensory disturbance noted on examination. Progressive muscular atrophy, weakness, and fasciculations of the upper extremities, shoulder girdle, and neck began eight months after initial presentation. Thereafter, he developed flaccid paralysis of the upper extremities and a head drop. A Babinski's sign was present bilaterally.

Cerebrospinal fluid (CSF) contained 5×10^3 lymphocytes/litre and 830 mg protein/litre. There were no atypical lymphocytes or tumour-like cells noted in the CSF. IgM titres for herpes simplex were negative. Muscle computed tomography at the level of C5 demonstrated severe muscular atrophy of the limb, shoulder girdle, paraspinal, and thoracic muscles. Electromyogram studies showed neurogenic changes in the muscles of the upper extremities and shoulder girdle, including the deltoid, biceps, triceps, scapular, and upper paraspinal muscles, and no changes to the muscles of the lower extremities and pelvic girdle. The results of a nerve conduction study, including sensory and motor evoked potentials, were within the normal ranges for all extremities.

Brain MRI revealed high signal intensity in the grey matter of the right frontal and bilateral mesial temporal lobes (fig 1A, B). T2 weighted MRI revealed high signal intensity in the grey matter of the cervical spinal cord (fig 1C, D). Serum and CSF were positive for the anti-Ma2 antibody confirmed by the binding to the recombinant Ma-2 protein, but were negative for anti-Ma1, anti-Hu, and anti-Yo antibodies (fig 2A, B). Thus, the patient was diagnosed as having an anti-Ma2-associated paraneoplastic neurological syndrome. The patient was treated with two courses of intravenous immunoglobulin (2.5 g/day for five days), followed by intravenous methylprednisolone (1 g/day for three days) during which the patient showed clinical improvement. The patient stabilised and progression of the muscular atrophy ceased, although he continued to have severe flaccid paralysis of the upper extremities and a head drop. The symptoms of amnesia, irritability, overall cognitive decline, hypersomnia, and vertical gaze palsy also remained unchanged. The patient was subsequently treated with antiepileptic medication to prevent further seizure activity. Brain MRI abnormalities resolved after the course of treatment, but the MRI cervical cord lesion remained.

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

Figure 1 (A, B) The magnetic resonance imaging (MRI) fluid attenuated inversion recovery image on admission demonstrated a high signal intensity in the bilateral mesial temporal lobe, right frontal cortex, and right insula. There was no enhancement by gadolinium-DTPA (diethylene triamine pentaacetic acid). These abnormal signal lesions disappeared following treatment with intravenous immunoglobulin and steroids. (C, D) T2 weighted MRI demonstrated a symmetrical high signal lesion (arrow), which was relatively confined to the grey matter of the cervical spinal cord. The lesion was not enhanced by gadolinium-DTPA.

Figure 2 (A) Western blotting analysis showed that the patient's serum reacts with the 40 kDa protein band representing recombinant Ma-2 protein. (B) Immunostaining using the patient's serum and rat cerebrum shows nucleolar rather than nuclear staining.

DISCUSSION

We report the case of an anti-Ma2 associated paraneoplastic neurological syndrome in a patient with a history of testicular germ cell tumour who presented with encephalitis and motor neurone disease-like features. T2 weighted MRI of the cervical spinal cord showed a well confined high signal intensity lesion, which correlated with the extensive muscular atrophy and weakness.

Dalmau *et al* studied the clinical findings of 38 patients with anti-Ma2-associated encephalitis.⁶ They reported that eye movement abnormalities were prominent in 92% of the patients with brainstem dysfunction, and 60% of these patients had vertical gaze paresis. Among 34 patients with cancer, 18 had testicular germ cell tumours. They concluded that anti-Ma2 encephalitis should be suspected in patients with limbic, diencephalic, or brainstem dysfunction who have MRI abnormalities in these regions and CSF inflammatory changes. In young male patients who present with paraneoplastic neurological syndromes, the primary tumour is usually located in the testis.⁶ Dalmau *et al* also described a 58 year old man with adenocarcinoma of the lung, who developed proximal weakness, muscular atrophy, and fasciculations of the upper extremities without evidence of MRI abnormalities in the brain or spinal cord.⁶ Our patient's presentation was characterised not only by encephalitis, but

also by motor neurone disease-like clinical features, which are probably attributable to the cervical spinal cord lesion.

Although it remains unclear whether the anti-Ma2 antibody associated with testicular germ cell tumours is directly involved in the pathogenesis of encephalitis and cervical spinal cord lesions, the response to immunomodulatory treatments such as intravenous immunoglobulin and steroids supports the idea that anti-Ma2 has anti-tumour immune activity.

Our case supports the unique clinical diversity of the anti-Ma2-associated paraneoplastic neurological disorder.

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REFERENCES

- 1 **Voltz R**, Gultekin SH, Rosenfeld MR, *et al.* A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. *N Engl J Med* 1999;**340**:1788–95.
- 2 **Barnett M**, Prosser J, Sutton I, *et al.* Paraneoplastic brain stem encephalitis in a woman with anti-Ma2 antibody. *J Neurol Neurosurg Psychiatry* 2001;**70**:222–5.
- 3 **Rosenfeld MR**, Eichen JG, Wade DF, *et al.* Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. *Ann Neurol* 2001;**50**:339–48.
- 4 **Sahashi K**, Sakai K, Mano K, *et al.* Anti-Ma2 antibody related paraneoplastic limbic/brain stem encephalitis associated with breast cancer expressing Ma1, Ma2, and Ma3 mRNAs. *J Neurol Neurosurg Psychiatry* 2003;**74**:1332–5.
- 5 **Scheid R**, Lincke T, Voltz R, *et al.* Serial 18F-fluoro-2-deoxy-D-glucose positron emission tomography and magnetic resonance imaging of paraneoplastic limbic encephalitis. *Arch Neurol* 2004;**61**:1785–9.
- 6 **Dalmau J**, Graus F, Villarejo A, *et al.* Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;**127**:1831–44.

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