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# Anti Ma2-associated myeloradiculopathy: expanding the phenotype of anti-Ma2 associated paraneoplastic syndromes

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## Abstract

Anti-Ma2 associated paraneoplastic syndrome usually presents as limbic encephalitis in association with testicular tumours.[1, 2] Only four patients have been reported with involvement outside the CNS, two of whom also had limbic or brainstem encephalitis.[2, 3] We report a man with anti- Ma2 associated myeloradiculopathy and previous testicular cancer whose neurological syndrome stabilised and anti-Ma2 titres fell following orchidectomy of a microscopically normal testis.

## Case Report

A 46-year-old dentist noticed weakness of pincer movement in the left hand. Six weeks later he developed sequential finger drop of the 4th, 5th and 3rd fingers of the left hand over days. During the subsequent weeks the fingers of his right hand also dropped. He had a prior

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history of left orchidectomy for stage I testicular seminoma and had been well on surveillance for 5 years. MRI brain, cervical spine and brachial plexii were normal. A diagnosis of multifocal motor neuropathy with conduction block was considered. Neurophysiology of the upper limbs demonstrated reduced motor amplitudes and acute and chronic denervation but no conduction block. Neurophysiology of the lower limbs was normal. He was given a trial of intravenous immunoglobulin without response. Some weeks later he developed an unusual itchy sensation spreading across his back and shoulders.

On examination there was head drop with weakness of neck flexion. There was wasting of both forearms and intrinsic hand muscles, with some fasciculations in the biceps and triceps. Tone was normal. There was asymmetric patchy proximal and distal weakness of both arms with finger drop. Reflexes were brisk in the upper limbs. He described an abnormal `spreading out' sensation to pinprick in a cape-like distribution. Neurological examination of the lower limbs was normal, as was general examination. In particular, there were no testicular masses or lymphadenopathy.

The combination of the lower motor neuron upper limb syndrome with a capelike sensory disturbance as well as the neurophysiological findings suggested a cervical myeloradiculopathy.

Blood count, electrolytes, erythrocyte sedimentation rate, C reactive protein, antineutrophil cytoplasmic antibodies, rheumatoid factor, cryoglobulins, B12, HIV, a-fetoprotein, human chorionic gonadotrophin, Lactate dehydrogenase, Brucella serology, Treponemal serology, Lyme serology and GM1 IgM antibodies were all normal or negative. Recombinant immunoblotting was negative against Hu/Yo/Ri/CV2/amphiphysin/ Ma1 antibodies but was positive against Ma2 (detectable at a serum dilution of 1:10 000, figure 1). CSF was acellular with normal protein; however, unmatched oligoclonal bands were present.

Repeat MRI of the brain, cord and brachial plexii and testicular ultrasound were normal, as was full body fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT.

Given the strongly positive anti-Ma2 antibody titre, history of previous testicular seminoma and absence of another cause of myeloradiculopathy, a paraneoplastic syndrome was suspected. As he continued to deteriorate, he was treated with high dose steroids which slowed the rate of clinical decline. He then received plasma exchange after which the sensory symptoms improved; however, slow deterioration continued in his strength and anti-Ma2 titre remained high. Adjuvant chemotherapy and/or orchidectomy were considered for occult disease. As his risk of seminoma recurrence at 5 years was considered <1% while the risk of a second primary testicular tumour was>5%, he underwent a right orchidectomy. Histology of the testis was normal despite a thorough search for tumour. However, intriguingly, following surgery, the anti-Ma2 antibody titre dropped to 1:10, upper limb strength stopped deteriorating and he is neurologically unchanged at 1 year follow-up. As he stabilised and no tumour was found, adjuvant chemotherapy was not given.

## Comment

We have reported a young man with an anti-Ma2 associated paraneoplastic myeloradiculopathy, presumably related to occult testicular tumour in the remaining testis. His neurological syndrome stabilised after orchidectomy of a microscopically normal testis and anti-Ma2 antibody titres fell. Although we could not demonstrate a tumour in the removed testis, his disorder fulfils criteria for a definite paraneoplastic syndrome, being associated with well characterised onconeuronal antibodies (anti-Ma2). The fact that his neurological syndrome stabilised and anti-Ma2 titres fell after orchidectomy offer further

supportive evidence that the paraneoplastic syndrome and anti-Ma2 antibodies were due to occult testicular tumour.

Anti-Ma2 antibodies recognise an onconeuronal protein PNMA2, which has been shown to be expressed in neurons of the brain and spinal cord, dorsal root ganglia, intestinal autonomic neurons and adrenal medullary ganglion cells, as well as in tumours.[4] Thirty-eight cases of anti-Ma2 associated paraneoplastic syndromes have been reported to date.[1–3, 5] Tumours were found in 34 patients (89%), the majority of which were germ cell tumours in young men.[1, 2] Limbic encephalitis and brainstem/cerebellar syndromes were the most common manifestations and most (82%) did not develop a tumour until after the onset of the paraneoplastic syndrome.[2]

Only four cases of anti-Ma2 associated paraneoplastic syndromes have been reported with involvement outside the CNS. One patient presented with limbic encephalitis but developed progressive atrophy of the upper limbs with head drop 6 months post bilateral orchidectomy for germ cell tumour. MRI showed high signal within the mesial temporal lobes and cervical cord.[3] Another patient presented with polyneuropathy 14 years after orchidectomy; nerve biopsy showed chronic inflammation.[2] A third patient presented with gait difficulties and was found to have a mixed upper and lower motor neuron syndrome without any evidence of tumour; MRI was not performed.[2] The fourth patient developed wasting, weakness and hypoaesthesia of both upper limbs 14 months after a diagnosis of lung adenocarcinoma; he also developed a brainstem syndrome.[1] Thus myeloradiculopathy without CNS involvement, as in our patient, is a unique presentation of anti-Ma2 associated paraneoplastic syndrome.

Paraneoplastic syndromes are often associated with occult tumours, perhaps because the antibodies generated have an antitumour effect. Mathew et al described six men with anti-Ma2 associated paraneoplastic syndromes without preoperative evidence of testicular tumour who underwent orchidectomy. In one, intratubular germ cell neoplasm unclassified type (IGCNU, a common precursor of invasive cancer) was found at initial pathological examination; in four, IGCNU was only found after pathological reassessment and in one patient no tumour was found. Four of the six had stabilisation of their neurological syndrome post-orchidectomy.[6] Tumour was not found in our patient despite careful examination. One possibility is that extra-gonadal tumour was present, however full body FDG-PET/CT was normal and anti-Ma2 titres fell following orchidectomy, suggesting that the driver for antibody production was within the testis.

The underlying pathomechanism of anti- Ma2 associated paraneoplastic syndromes remains unclear. Pathological studies have documented inflammatory cell infiltrate in affected tissues, suggesting a possible interaction between humoural and T cell responses.[1, 2, 4]

Paraneoplastic anti-Ma2 associated neurological syndromes almost always present with limbic encephalitis or brainstem involvement. Myeloradiculopathy with normal imaging and without other CNS involvement expands the phenotype of anti- Ma2 associated paraneoplastic disorders. This report also demonstrates that orchidectomy may halt progression of anti-Ma2 associated paraneoplastic syndrome even in the absence of obvious testicular tumour.

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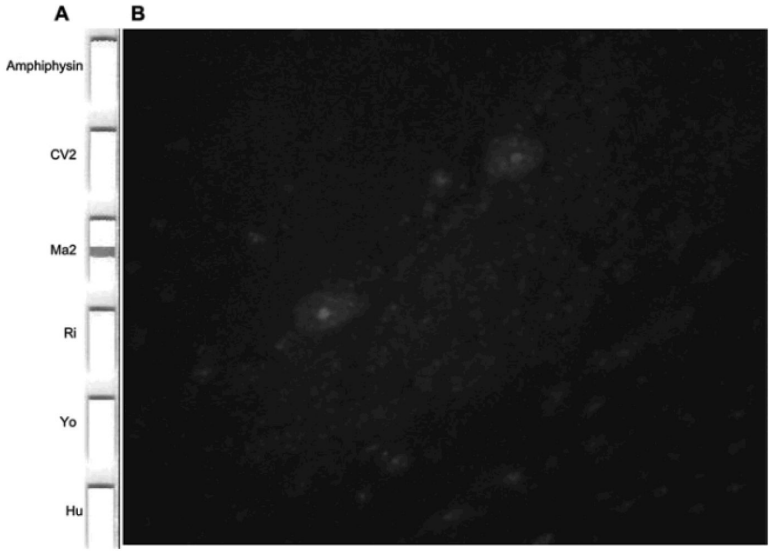


**Figure 1.**

(A) Western blot using the patient's serum demonstrates positive staining to Ma2 protein and negative to amphiphysin, CV2, Ri, Yo and Hu. (B) Immunostaining using the patient's serum and primate cerebellum demonstrates positive staining of Purkinje cell nucleoli (dilution 1:1600).