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BRIEF COMMUNICATION

Cancer and motor neuron disease—causal or coincidental? Two contrasting cases

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Abstract

Introduction Motor neuron disease (MND) can occur in patients with cancer, but there is minimal evidence that this is more than by chance. We contrast two cases of motor neuronopathies occurring in the context of systemic malignancy and argue that in one case the cause was most likely paraneoplastic, while in the other it was not.

Case 1 A 61-year-old woman developed progressive walking difficulties over 9 months with weakness and stiffness in her legs. EMG showed fibrillations and positive sharp waves in multiple lower limb muscles bilaterally, with neurogenic units and a reduced recruitment pattern. An invasive ductal carcinoma of the breast was identified and she continued to deteriorate neurologically with worsening mobility, upper limb spasticity and fasciculations. She died approximately 26 months after symptom onset.

Case 2 A 57-year-old woman developed weight loss and weakness of her right arm without any sensory symptoms. At presentation, she had wasting and fasciculations in her right upper limb muscles, with normal reflexes, normal left upper limb and lower limb examination. Over the following week, she developed left upper limb weakness and fasciculations, brisk knee reflexes, and flexor plantar responses. Her EMG showed upper and lower limb denervation. She was found to have anti-Hu and anti-CV2 antibodies present in serum. A PET-CT showed active uptake in lymph nodes in the right hilum. Biopsy confirmed a small cell lung cancer. She had chemoradiation therapy and the tumour went into remission. She has remained well on follow-up 24 months later, regaining weight and strength after her chemotherapy. She continues to be monitored for cancer recurrence, but thus far appears to be in remission.

Conclusion In cases with rapidly progressive MND, particularly of upper limb onset, consideration should be given to testing anti-neuronal antibodies and searching for an occult tumour.

Keywords Motor neuron disease · Amyotrophic lateral sclerosis · Cancer · Paraneoplastic · Upper motor neurone signs · Lower motor neurone signs

Abbreviations

MND	motor neuron disease
ALS	amyotrophic lateral sclerosis
NCS	nerve conduction studies
EMG	electromyogram
PET	positron emission tomography
MRI	magnetic resonance imaging
CT	computed tomography

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PNS paraneoplastic neurological syndrome
CSF cerebrospinal fluid

Introduction

Motor neuron disease (MND) is normally felt to be a neurodegenerative disorder. The revised criteria for the diagnosis of the most common phenotype, amyotrophic lateral sclerosis (ALS), reports an association with ALS and lymphoma, but that when associated with other cancers, these are not felt to be causal [1]. The criteria suggests neuroimaging be arranged to exclude other causes for the clinical presentation, but not systemic imaging or routine paraneoplastic antibody testing [1]. Motor neuron disease can occur in patients with cancer, but there has been minimal evidence that this is more than by chance. Therefore, clinicians do not generally investigate for the potential of an underlying causal paraneoplastic syndrome.

We contrast two cases of motor neuronopathies occurring in the context of systemic malignancy and argue that in one case the cause was most likely paraneoplastic, while in the other it was not.

Case 1

A 61-year-old woman developed progressive walking difficulties over 9 months with weakness and stiffness in her legs. She had no sensory symptoms. She had brisk reflexes throughout and flexor plantar reflexes. MR imaging of head and spine showed minor non-specific white matter changes only. Serum was negative for anti-Hu, -Yo, -Ri, -SOX1, -Titin, -Recoverin, -Ma2/Ta, -CV2, and -amphiphysin antibodies. NCS showed normal motor and sensory responses. EMG showed fibrillations and positive sharp waves in multiple lower limb muscles bilaterally, with neurogenic units and a reduced recruitment pattern.

An invasive ductal carcinoma of the breast was identified and she continued to deteriorate neurologically with worsening mobility, upper limb spasticity and fasciculations. The patient was counselled that although her motor neuronopathy and breast cancer were unlikely to be related, that there were reported cases implicating cancer as potentially causal. After detailed discussion of her treatment options, she elected for the tumour to be treated by mastectomy and lymph node clearance, followed by radiotherapy and letrozole therapy.

Despite treatment of the tumour, the patient continued to deteriorate over several months, with worsening limb function and bulbar involvement. She died approximately 26 months after symptom onset.

Case 2

A 57-year-old woman developed weight loss and weakness of her right arm without any sensory symptoms. At clinical presentation, 4 weeks from onset, she had wasting and fasciculations in her right upper limb muscles, with normal reflexes, normal left upper limb and lower limb examination. Over the following week, she developed left upper limb weakness and fasciculations, brisk knee reflexes and flexor plantar responses. She had no cranial nerve involvement. MR imaging was normal. Nerve conduction studies were normal. EMG showed active denervation in all 5 upper limb muscles tested bilaterally, in the right thoracic paraspinals and in left tibialis anterior. Fasciculations were present in the right trapezius muscle.

She was an ex-smoker and was found to have anti-Hu and anti-CV2 antibodies present in serum. A CT of her chest, abdomen and pelvis was normal. A PET-CT showed active uptake in lymph nodes in the right hilum. Biopsy confirmed a small cell lung cancer. She had chemoradiation therapy and the tumour went into remission. Her upper and lower limb function improved, and having been immobile at diagnosis with significant weakness in all four limbs, she regained independent mobility with the use of an ankle foot orthosis for her left ankle. She has remained well on follow-up 24 months later, regaining weight and strength after her chemotherapy. She continues to be monitored for cancer recurrence, but thus far appears to be in remission.

Discussion

Paraneoplastic neurological syndromes (PNS) comprise a disparate group of distinct neurological disorders that are the remote effect of the immune response to a malignancy. MND is not usually included in discussions of PNS[2] because there is a limited number of case report of co-existing MND-like disorders and cancer, with epidemiological studies showing little evidence of an association [3, 4]. Various studies have argued that routinely screening MND cases for anti-neuronal antibodies is of no value [5, 6]. Nonetheless, there is some evidence from case reports that in very rare instances, motor neuronopathies can be a paraneoplastic phenomenon [7].

The most suggestive phenotype is in those with a rapidly progressive deterioration, associated with anti-Hu antibodies as reported in three cases in 1997 [8]. There were two further reported cases presenting with a bilateral upper limb onset of weakness, widespread upper limb denervation and positive anti-Hu antibodies [9, 10]. These patients were also found to have small cell lung cancers. One had additional signs of dysautonomia [10]. Sadly, both succumbed to their condition despite immunotherapy. A recent French series identified eight cases of probable paraneoplastic MND out of 2200

consecutive cases diagnosed with MND over a 5-year period of time in one centre [11]. Seven patients were found to have anti-Hu and one anti-Yo antibodies and supportive clinical and electrophysiological findings. Five (62.5%) of these patients presented with upper limb weakness and seven (88%) had an onset and evolution within 2 months [11]. Two had the additional finding of a sensory neuronopathy. Following cancer treatment and immunoglobulin five (62.5%) were reported to be in remission [11].

Conclusion

In cases with rapidly progressive MND, particularly of upper limb onset, consideration should be given to testing anti-neuronal antibodies and searching for an occult tumour. While the historic literature saw poor outcomes in similar cases associated with small cell lung cancer, the potential for early recognition and improvements in cancer treatment outcomes makes recognition therapeutically important. The presence of well-characterised anti-neuronal antibodies and clinical stabilisation supports a paraneoplastic cause in case 2. The potential for remission of both the cancer and progressive motor neuronopathy makes early recognition and treatment vitally important. However, the routine testing of anti-neuronal antibodies in all patients with motor neuronopathy is not justifiable. Especially, when considering that anti-Hu antibodies, for example, occur in 2% of patients without cancer [12]. It is important to recognise in counselling patients like case 1, with a concomitant diagnosis of malignancy and motor neuronopathies that it is more common for these to be unrelated. In such cases, it is important to consider the potential negative impact of cancer therapies on their prognosis. Similarly, the use of immunotherapy is unlikely to be justified without supportive biomarkers such as positive anti-neuronal antibodies, CSF pleocytosis or CSF-restricted oligoclonal bands [11].

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Author contributions JG produced the first draft of the paper. GG provided the background information on the literature relating to the epidemiology of cancer in MND. VL undertook neurophysiology studies on both patients and summarised the results for the paper. SP summarised the clinical information for case 2. GM identified the two cases and revised, edited and submitted the paper for publication. All of the authors listed have read and approved the final manuscript.

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Compliance with ethical standards

Consent to publish We have obtained written consent from the next of kin of patient one, and from patient two, herself for publication.

Competing interest The authors declare that they have no competing interests.

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