Rare disease

Paraneoplastic ataxia and dystonia secondary to a malignant fibrous histiocytoma

Ross Dolan,¹ Ralph Thomas,² Jonathan I O'Riordan³¹ Department of Neurology, University of Dundee, Dundee, UK² Division of Clinical Neurosciences, Western General Hospital, Edinburgh, UK³ Department of Neurology, Ninewells Hospital, Dundee, UKCorrespondence to Ross Dolan, rdolan@nhs.net

Summary

Paraneoplastic movement disorders are part of the spectrum of paraneoplastic syndromes caused by the production of onconeural antibodies such as anti-Hu by underlying tumours. These attack specific neurons depending on receptor aetiology. We report the case of a 53-year-old man who presented 8 years previously with symptoms of upper limb weakness, light headedness, dizziness and falls. His condition followed a progressive course. Two years after onset he had right-sided weakness, diplopia and generalised dystonia. Initial investigations identified a positive anti-Hu antibody, but an extensive search for a primary tumour was negative. A malignant fibrous histiocytoma in his right gluteal fold was subsequently identified. At this stage he was bed bound with severe ataxia, dystonia and spasticity. Following surgical excision and treatment with high dose steroids and pulse immunoglobulin, further progression was arrested and minor improvements occurred. He can now ambulate with bilateral assistance but remains severely disabled.

BACKGROUND

To our knowledge only three other cases of paraneoplastic syndrome due to a primary malignant fibrous histiocytoma, previously known as a pleomorphic sarcoma, have been reported in the literature. However this is the first case with both pathological confirmation and positive onconeural antibody serology for anti-Hu. It was felt at an early stage that our patient had a paraneoplastic disorder, but an extensive screen of known primaries proved fruitless. The rarity of this patient's condition suggests that in the context of a presumed paraneoplastic disorder, a muscle primary should be considered. This case adds to our clinical knowledge and highlights the importance of considering paraneoplastic syndrome particularly from unusual tumour sites as a plausible explanation for patients presenting with progressive multifocal neurodegeneration.

CASE PRESENTATION

A 53-year-old male forester presented 8 years previously with headache, dizziness, vertigo and weakness in his upper limbs. He continued to show further progressive neurological deterioration which began to affect his lower limbs, resulting in unsteadiness and several falls. There were square wave eye jerks and impairment of external ocular movement accompanied by diplopia. Higher cortical function was preserved. His speech deteriorated, resulting in substantial difficulties in communication. The initial symptoms suggested a brainstem and extrapyramidal disorder and demyelination was considered. Initial MRI of the brain and cervical spine was normal. Oligoclonal bands were detected in the cerebrospinal fluid (CSF) but not in the serum, suggesting an inflammatory or immune mediated disturbance. He continued to deteriorate, developing a combination of cerebellar, pyramidal and basal ganglia

abnormalities. There was head and neck dystonia and ocular convergent spasm. He had severe ataxia and tremor with unintelligible speech. There was generalised hypertonia over and above obvious limb dystonia, hyperreflexia and an extensor plantar. Responses to pin-prick sensation were diminished distally with preservation of proprioception and vibration sensation. Immunohistochemistry revealed positive anti-Hu antibodies, suggesting a paraneoplastic disorder. An extensive search for a primary tumour included repeated MRI of brain and spinal cord, CT imaging of thorax, abdomen and pelvis and positron emission tomography (PET) scanning, but all were normal or negative.

Three years after his initial presentation he developed a slowly enlarging painful egg-sized swelling over the right gluteal fold. Biopsy identified a pleomorphic malignant fibrous histiocytoma. Further analysis showed the tumour to be anti-Hu positive, confirming a connection between the excised tumour and his neurological deterioration. As a result he underwent an extensive excision.

Repeat imaging confirmed no metastatic deposits elsewhere. His condition has stabilised and despite some improvement following intravenous immunoglobulin, he remains severely disabled requiring continuous care and bilateral assistance for ambulation.

INVESTIGATIONS

MRI of the brain and whole spinal cord on two separate occasions was normal. CT and PET scans proved to be unremarkable, showing no signs of focal abnormality, cerebrovascular disease, demyelination or metastatic tumour deposits. EEG recordings were normal. Electromyography recordings showed evidence of a generalised dystonia with additional denervation in C5 derived muscles. This latter finding was thought to be secondary to the severe postural

Figure 1 Flow chart of diagnostic evidence of paraneoplastic neurological syndromes.⁴

changes in the cervical spine as a result of the dystonia. There was no associated neuropathy. Spinal fluid examination demonstrated oligoclonal bands in the CSF which were absent from the serum. HIV and syphilis serology was negative. Pathological analysis of the excised right gluteal mass showed it to be a malignant fibrous histiocytoma which was anti-Hu positive, suggesting a paraneoplastic component.

DIFFERENTIAL DIAGNOSIS

Paraneoplastic movement disorder
Lyme disease
Brainstem demyelination
Cerebral vasculitis
Neurological complications of HIV and syphilis
Variant CJD.

TREATMENT

The mass on the right gluteal fold was fully excised. The patient did not require subsequent radio or chemotherapy. Spasticity was treated with oral baclofen and intermittent botulinum toxin injection, while supportive therapy was provided with occupational and physiotherapy. He received high dose steroids without any appreciable benefit. Subsequent pulsed intravenous immunoglobulin resulted in stabilisation and marginal improvement.

OUTCOME AND FOLLOW-UP

The patient remains severely disabled but has not changed much over the past 5 years.

DISCUSSION

Paraneoplastic disorders are a relatively rare condition where substances secreted by both benign and malignant tumours can have effects on different bodily systems often far removed from the anatomical location of the causative tumour.¹ Paraneoplastic tumours can affect a wide range of systems including the endocrine, renal, haematological, gastrointestinal and, as in this case, the neurological sys-

tems and in many cases the paraneoplastic signs and symptoms can present before the initial primary tumour has been identified.²

This patient presented with a progressive neurological disorder which at the onset was felt to be paraneoplastic in origin. This led to an extensive search for a primary causative tumour, which for 3 years was negative. It was not until a mass appeared in the gluteal region that the tumour was identified and treated and the patient's condition stabilised.³ There are now internationally accepted diagnostic criteria for paraneoplastic syndromes which have been summarised in figure 1.⁴ This divides presentations into classical and non-classical forms.^{3 4} The list of classical syndromes includes encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, stiff person syndrome, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, Lambert-Eaton myasthenic syndrome and dermatomyositis.^{3 4} In our case the patient had cerebellar dysfunction with dysarthria, impaired coordination, nystagmus and a loss of smooth pursuit eye movements.^{5 6} Over and above this, however, he had spasticity and dystonic posturing, supporting a diagnosis of paraneoplastic cerebellar degeneration with additional dystonic features. We did not consider any definite evidence of a brain stem encephalitic process. He therefore does not fall into the classical category. The spasticity has some hallmarks of stiff person syndrome, again a classical paraneoplastic disorder, but antiglutamic acid decarboxylase (GAD) antibodies were negative. In paraneoplastic stiff person syndrome there is axial rigidity and intermittent painful spasms.³ There is a strong correlation with encephalomyelitis and autoantibodies against GAD are positive in 50–90% of cases.³ Our patient, therefore, was non-classical. Finally, the fact that there was a confirmed tumour and positive serology for the onconeural antibody anti-Hu makes the diagnosis of paraneoplastic syndrome with an associated movement disorder definite.

Paraneoplastic movement disorders have been widely reported in the literature, however overall they are relatively rare conditions, affecting fewer than 1/10 000 cancer patients.¹ The vast majority of anti-Hu positive paraneoplastic tumours are small cell lung cancers. Extensive imaging using both CT and MRI scanning failed to show any evidence of this in our patient, however, he did have a malignant fibrous histiocytoma removed which was anti-Hu positive. To our knowledge only three similar cases have been reported in the literature. In 1992 Reinecke *et al*⁷ described a patient with a paraparesis due to a malignant fibrous histiocytoma previously known as a pleomorphic sarcoma. There was no evidence of metastases and the presumption was that the paraparesis was paraneoplastic in nature.⁷ In 2004 Zámečník *et al*⁸ reported a the case of a 77-year-old woman with opsoclonus-myoclonus. Her symptoms deteriorated rapidly and she entered a coma and died several months later.⁸ At autopsy a pleomorphic sarcoma in the retroperitoneum was found with no evidence of metastatic spread.⁸ Microscopic examination of the cerebellum showed atrophy of the granular layer accompanied by severe patchy loss of Purkinje cells, and neuronal loss in the cerebellar nuclei with distinct peridental demyelination and astrogliosis.⁸ Unfortunately, the investigating pathologist was unable to confirm the presence of any known onconeural antibodies in the CSF or serum, but the autoimmune nature of the disease was confirmed by the presence of oligoclonal bands in CSF and the immunohistochemical detection of immunoglobulin G deposits on membranes of Purkinje cells, neurons of cerebellar granular layer and in the cerebellar nuclei.⁸ Also in 2004 Corato *et al*⁹ reported a case of paraneoplastic brainstem encephalitis in a patient with a malignant fibrous histiocytoma with atypical antineuronal antibodies. In this case, a 74-year-old man presented with a 2-month history of myoclonus affecting the upper extremities and with increased tendon reflexes on the right.⁹ An abdominal CT revealed a retroperitoneal mass with multiple hepatic and lymphatic formations with biopsies of the lateral aortic lymph node confirming the presence of a malignant fibrous histiocytoma which was shown to be producing atypical antineuronal antibodies by a combination of immunohistochemical and western blot analysis.⁹

In conclusion, this is the first case of a paraneoplastic syndrome due to a malignant fibrous histiocytoma with confirmed pathological evidence and a positive onconeural antibody serology for anti-Hu. It highlights the importance of looking for unusual and unexpected primary tumours in paraneoplastic syndrome. The time-scale from initial presentation until a confirmed diagnosis was over 3 years. Clinicians should be aware of this and if they suspect paraneoplastic syndrome, screening using standard imaging

techniques may be required. The identification of the primary tumour is essential as the best way to treat paraneoplastic disorders is to remove the source of the problem by excising the causative tumour.¹

Learning points

- ▶ While the majority of paraneoplastic tumours are small cell lung cancers, other less common tumours such as malignant fibrous histiocytomas should be considered.
- ▶ The time course from initial presentation to the identification of the primary causative tumour can be quite long, which can present a challenge in terms of patient management.
- ▶ Identification and removal of the causative tumour is essential as it is the only proven method of arresting paraneoplastic neurodegeneration.
- ▶ Paraneoplastic disorders can lead to severe physical disability often with preserved higher cortical functions, meaning that a holistic approach to patient care is necessary, with adequate home support and a community care package being essential.
- ▶ When screening for possible underlying neoplasia, one needs to consider sites other than simply the thorax, abdomen and pelvis.

Competing interests None.

Patient consent Obtained.

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