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LETTER TO THE EDITOR

''Flail arm syndrome'' with anti-Hu antibodies

Síndrome del ''hombre en barril'' con anticuerpos anti-Hu

Dear Editor,

Motor neuron diseases (MND) do not constitute one of the classically established paraneoplastic neurological syndromes (PNS). Most published examples are of single cases or small series, with a minimal evidence that this is more than chance.[1] Herein, we describe the case of a 63-year-old woman with lower motor neuron disease and anti-Hu antibodies who developed a lung neoplasm and autonomic symptoms.

A 63-year-old woman with a history of smoking, thoracic hyperkyphosis and severe pulmonary emphysema is admitted into the intensive care unit due to a respiratory infection requiring intubation and mechanical ventilation. In this context, after presenting a favorable evolution she was assessed by neurologists to complete a 7-month progressive weakness study in both upper extremities that began asymmetrically. In addition, she reported having lost 10 kg in the last 6 months. Neurological examination revealed weakness in the neck extensor muscles and a severe weakness of the upper limbs, both proximal and distal, with inability to raise both arms. Atrophy of the shoulder girdle and intrinsic muscles of both hands was observed without visible fasciculations. She also had generalized arreflexia with normal superficial sensitivity and no upper motor neuron signs.

Cervical MRI revealed no significant foraminal or canal stenosis. Blood tests were normal including serologies and serum immunofixation. High titers of ANA and high titers of anti-Hu antibodies were detected (Western Blot technique). The biochemical analysis of the cerebrospinal fluid was normal. Electrodiagnostic findings show extensive neurogenic involvement predominantly in the cervical and thoracic region, with signs of ongoing denervation/reinnervation and massive loss of motor units, without signs of segmental demyelination or sensory neurographic involvement. Whole-body PET-CT scan detected a 10 mm diameter hypermetabolic pulmonary nodule in right upper lobe, suggestive of malignancy. See Fig. 1.

A course of intravenous immunoglobulin 0.4 g/kg/day was administered for 5 days, with no effect on the neurological condition. The case was presented to a multidisciplinary committee, deciding on radiotherapy treatment given the high surgical risk and the impossibility to perform needle biopsy given the deep location of the lesion and the anatomical characteristics.

After 8 months we observed a progression of the neuromuscular disease, with functionality loss of the upper limbs and development of weakness of the lower limbs, making her unable to stand and walk, with no other signs of the first motor neuron. However, in the control CT scan, the nodule had decreased in size (3 mm × 4 mm). The patient was admitted 4 months later due to a 2-week history of constipation, with a large dilated loop observed on the abdominal CT scan, diagnosing paralytic ileus. During this admission, the patient presented deterioration in her general condition, with bronchial aspiration, so it was decided together with the relatives to limit the therapeutic effort, and she finally died during admission.

Various studies have argued that routinely screening MND cases for anti-neuronal antibodies is of no value.[2,3] Nevertheless, few case series have reported well-characterized onconeuronal antibodies in patients with MND, and the pathophysiology of these onconeuronal antibodies is disputed. A recent review by Tolkovsky et al. has analyzed the 17 cases described in the literature about MND and anti-Hu.[4] The most common phenotype was women with pattern of ''flail arm syndrome'' with anti-Hu antibodies and SCLC, as in our case. In most of these patients, lung cancer was diagnosed within a year of the onset of neurological signs.[4–7] However, most patients responded little or not at all to immunotherapy and tumor treatment, except in 2 cases that improved after chemoradiotherapy.[4,6]

In our case, we do not have a pathological diagnosis, but due to the PET characteristics uptake and association with Hu antibodies, the most probable diagnosis was SCLC. Some authors consider that the presence of anti-Hu antibodies in serum could be a marker of SCLC. In this study by List M et al., all patients evaluated with positive anti-Hu antibodies had SCLC.[8] On the other hand, Dalmau J et al. evaluated the presence of anti-Hu antibodies in patients with SCLC and healthy subjects. It was found that all those who presented paraneoplastic syndrome had positive anti-Hu and those who did not present paraneoplastic syndrome had positive anti-Hu 7/44 patients. No healthy subject presented anti-Hu antibodies. The anti-Hu antibodies appears, when present, to be a good marker for SCLC.[9]

In addition, we must consider the autonomic involvement that our patient had, with the development of a paralytic

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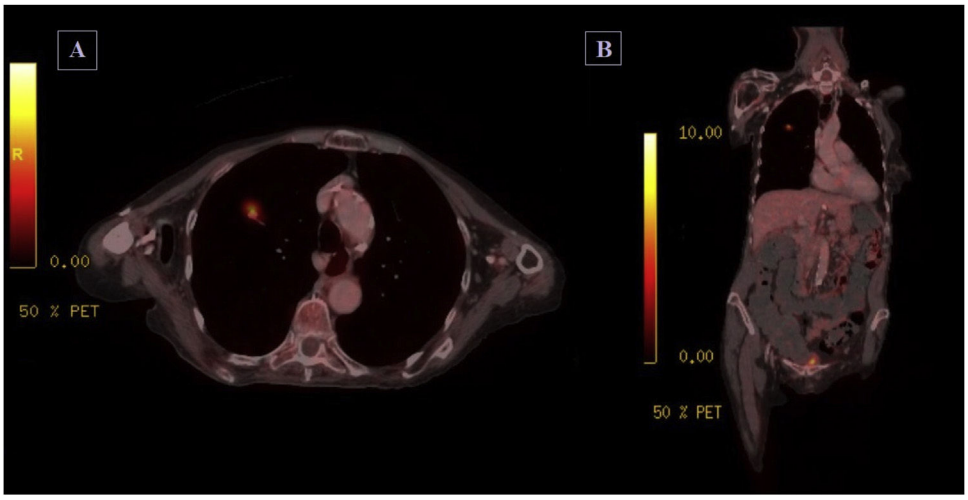

Figure 1 PET-CT images (Positron emission tomography co-registered with computarized tomography). Axial (A) and coronal (B) sections. Hypermetabolic pulmonary nodule in the right upper lobe, suggestive of malignancy.

ileus. This could be related to enteric neuropathy in the context of anti-Hu antibodies, although its appearance is not rare as a complication of seriously ill and bedridden patients. Dysautonomia is described in PNS associated with anti-Hu antibodies[10] and has also been described only in one case of 32-year-old woman with brachial amyotrophic dyparesis with anti-Hu antibodies,[11] with no other cases described in the literature, apart from our case.

Although PMND is considered a non-classical syndrome, the PNS diagnostic criteria proposed by Graus et al.[12] allow us to diagnose a ''definitive PNS'' in the presence of a well-characterized onconeuronal antibody, even in the absence of a classical clinical syndrome.

In conclusion, our case indicated a possible link between antineuronal antibodies and MND, but further investigations are required to evaluate their pathophysiological significance.

Ethics

This article has been reviewed by the Ethical Review board of the Balearic Islands (CEI-IB). The confidentiality of the patient has been preserved (neither text nor images contain identification data nor dates) and the patient's husband has granted his consent for publication. Therefore, this CEI-IB authorizes its publication (IB 4898/22).

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Late-onset sporadic nemaline myopathy presenting as hypercapnic respiratory failure

Miopatía nemalínica esporádica de inicio tardío manifestándose como una insuficiencia respiratoria hipercápnica

Dear Editor,

Nemaline myopathy (NM) is a congenital myopathy that follows an autosomal dominant or recessive inheritance pattern. It is classified according to the age of onset and the severity of respiratory and muscle involvement. From an anatomical pathology viewpoint, NM is characterised by deposition of rod-like cytoplasmic inclusions (nemaline rods) that stain red on Gomori trichrome. These rod-like structures are mainly composed of α-actin and have been located at the level of the Z-band of the sarcomere in electron microscopy studies.[1,2]

In adults, NM may either be hereditary, with a slowly progressive course and symptomaticity in adulthood, or present in adulthood and progress subacutely, without a hereditary pattern. This sporadic adult-onset form, known as sporadic late-onset NM (SLONM), is characterised by onset after the age of 40 years and is frequently associated with monoclonal gammopathy of undetermined significance (MGUS) or may be diagnosed in the context of HIV infection.[3—7] A potentially fatal disease, SLONM constitutes a challenge for neurologists as this myopathy may be treatable, according to the available evidence on the response to immunotherapy.

We present the case of a patient with respiratory failure who presented nemaline rods in a muscle biopsy.

Our patient was a 57-year-old woman who was admitted to the pulmonology department due to hypercapnic respiratory failure requiring non-invasive mechanical ventilation (NIMV). She had presented sensorineural hearing loss since childhood. Questioned specifically about muscle function, she reported a 6-month history of proximal muscle weakness in the lower limbs. The neurological examination detected bilateral ptosis, neck extensor muscle weakness, and proximal limb muscle weakness (muscle strength 4/5). A laboratory analysis revealed a normal-to-low creatine kinase level (22—44 U/L). The neurophysiological study revealed a myopathic pattern in proximal muscles, with low-amplitude, polyphasic motor unit potentials and isolated positive sharp waves. Neurography and repetitive nerve stimulation detected no alterations. A biopsy of the deltoid muscle using the Gomori trichrome stain identified nemaline rods in most muscle fibres (Fig. 1).

Serum protein electrophoresis and immunoelectrophoresis did not detect monoclonal protein, and a serology test for HIV infection yielded negative results. A genetic panel for congenital myopathies ruled out mutations in the genes known to cause NM. The study incidentally detected a mutation, c.1229G>A; p.(Arg410His), in heterozygosis in the *MYH14* gene, located on chromosome 19. The patient was initially treated with intravenous immunoglobulins and subsequently started maintenance treatment with prednisone. She remains clinically stable at 18 months of follow-up but continues to require NIMV overnight.

SLONM is a rare muscle disorder with a heterogeneous clinical presentation; clinical onset as respiratory failure in adults is infrequent.[8,9] In nearly half of cases, SLONM is associated with presence of haematological disease, mainly MGUS and multiple myeloma, as well as HIV infection. HIV-related NM is characterised by absence of facial or respiratory involvement and favourable clinical response to immunosuppressive treatment.[4] SLONM associated with monoclonal protein has traditionally been considered to present poorer prognosis, and is characterised by severe weakness and muscle atrophy, dysphagia, and respiratory failure. However, recent evidence suggests that these patients may respond to intensive treatment with intravenous immunoglobulins followed by chemotherapy or autologous stem cell transplantation.[6,7,10]

Patients with SLONM do not present known mutations in NM-related genes. *MYH14* encodes non-muscle myosin heavy-chain, which is expressed across all tissues but mainly in skeletal muscle (the term ''non-muscle myosin'' aims to differentiate this ubiquitous form of myosin from muscle tissue—specific myosin). *MYH14* is associated with hereditary nonsyndromic sensorineural hearing loss. The *MYH14* mutation detected in our patient caused hearing loss, although *MYH14* mutations have been linked to complex phenotypes combining hearing loss with myopathy and peripheral neuropathy, following an autosomal dominant inheritance pattern.[11] The patient did not consent to familial cosegregation analysis; her mother also presented sensorineural hearing loss. Currently, this genetic variant must be considered to be of uncertain significance for NM.

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