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Letter to the Editor

Motor neuron disease as a treatment responsive paraneoplastic neurological syndrome in patient with small cell lung cancer, anti-Hu antibodies and limbic encephalitis

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Dear Editor,

Non-classical paraneoplastic neurological syndrome (PNS) may be identified and classified as “definite” and “probable” according to the antineuronal antibodies status and the presence or absence of an associated cancer [1]. Paraneoplastic motor neuron disease (PMND) is a rare, potentially treatable, non-classical PNS that may be undistinguishable from sporadic motor neuron disease (MND) [2].

We present the case of a 63-years old Caucasian male, who developed, in August 2017, a progressively worsening insomnia, short-term memory loss and apathy. Brain MR scan revealed T2/FLAIR hyper-intensity in both temporal lobes and he was diagnosed with limbic encephalitis (LE). After a complete oncological screening diagnosis of small cell lung cancer (SCLC) was made. Onconeural antibodies testing was not performed at the time. In September 2017 the patient was treated with CPPD and etoposide chemotherapy. A total body FDG-PET scan performed four months later demonstrated a complete regression of cancer. His neurological symptoms improved as well. In May 2018, the patient was admitted to our Unit for the subacute onset of tetraplegia, upper motor neuron (UMN) signs, massive muscular atrophy and fasciculations. Neither sensory nor cranial nerves involvement was noticed. Brain and spinal cord MR scans were unremarkable. Routine blood tests resulted within normal ranges. The electromyographic analysis revealed active and chronic denervation and diffuse fasciculations in three different regions, in a segmental, non-nerve distribution. The electroneurography documented a mild distal sensory neuropathy. Transcranial magnetic stimulation showed reduced motor evoked potentials amplitude in the upper and lower limbs. A slight increase in the cerebrospinal fluid (CSF) protein concentration (124 mg/dL, normal range 15–45 mg/dL) with normal cell count was observed; type III oligoclonal bands were detected. Anti-Hu antibodies were detected in both serum and CSF. A chest CT scan revealed neoplastic relapse. A PMND was suspected and treatment with intravenous immunoglobulins was started, leading to neurological stabilization and slight improvement of lower limbs motility. He was discharged from our Unit to start rescue radiotherapy, which led to partial oncological remission and concomitant neurological improvement.

To our knowledge, no other cases of both LE and PMND in patients with SCLC and anti-Hu antibody positivity have been reported. Our patient could be classified as a “probable ALS”, according to El Escorial criteria [3], since UMN and lower motor neuron (LMN) signs were present in at least two different regions; additionally, other diseases were excluded by means of neuroimaging and neurophysiology. Furthermore, our patient fulfilled the diagnostic criteria for “definite PNS” [1] since he presented a non-classical syndrome with well-characterized onconeural antibodies. The relation with oncological progression, the partial improvement after tumor treatment, and the previous diagnosis of definite PNS suggested a paraneoplastic pathogenesis of the MND.

The association of cancer and MND has been debated [4–6]. PMND has been described in patients with anti-Ma2 antibodies: Vogrig and colleagues [7] reported three cases of PMND with anti-Ma2 antibodies and analyzed seven similar cases from the previous literature.

All those cases were diagnosed with “definite PNS” since the neurological syndromes were associated with well-characterized onconeural antibodies. Seven out of ten patients had tumors: four testicular tumors, two lung tumors, and one pleural mesothelioma were reported. In the latter case PMND developed after immune checkpoint blocker therapy with Tremelimumab, even though MND progressed after treatment interruption.

Five patients presented a monophasic disease course with MND at the onset, while the others presented a biphasic course with limbic or diencephalic symptoms followed by signs, symptoms or neurophysiological evidence of motor neuron involvement. An improvement or a neurological stabilization was observed in all patients after first or second line immunotherapy and tumor treatment.

Although our patient shared the initial limbic involvement, the neurophysiological features and the response to immunotherapy with anti-Ma2 associated PMND, he never developed diencephalic symptoms nor he had been previously treated with immune check point blockers. Moreover our patient developed a second delayed PNS strictly related with tumor relapse; this temporal relation has not been reported in patients with anti-Ma2 PMND.

MND has already been described as second delayed PNS in patients with anti-Hu antibodies, nevertheless those patients did not present LE at onset nor cancer relapse occurred [8]. Our case shared the multifocal and progressive involvement of the neuraxis seen in paraneoplastic encephalomyelitis (PEM) associated with anti-Hu antibodies, in which LE and subsequent severe motor weakness has been described.

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However, while our patient fulfilled clinical and neurophysiological MND criteria, none of those cases diagnosed with PEM "had a syndrome that could be confused with MND" [9].

The peculiar clinical and electrophysiological phenotype of PMND has not been exhaustively described yet. Even if routine testing of anti-neural antibodies in MND is currently not recommended [10], a paraneoplastic origin should be promptly suspected at least in those patients with a previous neoplastic history, subacute onset, other concomitant PNS, inflammatory signs in the CSF, and clinical improvement or stabilization after treatment [2]. In those cases onco-neural antibodies screening is crucially relevant since PMND is a potentially treatable condition.

Conflict of interest

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

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