Paraneoplastic syndromes are unusual manifestations of malignant diseases. Lambert-Eaton myasthenic syndrome (LEMS) is a presynaptic disorder of neuromuscular transmission occurring as an autoimmune consequence of several cancers, in particular ovarian and lung tumours, these latter mostly consisting of small cell lung cancer (SCLC). Patients with SCLC may occasionally display the features of the anti-Hu syndrome, a rare disorder characterized by various combinations of paraneoplastic encephalomyelitis, limbic encephalitis, sensory neuropathy/neuronopathy, cerebellar degeneration and positive titres of anti-Hu antibodies. Lambert-Eaton myasthenic syndrome has been linked to large cell neuroendocrine carcinoma (LCNEC) of the lung only twice in English literature to date, but the association of this syndrome with paraneoplastic manifestations resembling the anti-Hu syndrome and LCNEC had not been described so far.

A 56-year-old man was referred for difficulty in speech and progressive clumsiness. His wife reported delusional ideation, rapidly evolving over a few weeks. We interpreted the behavioural disturbance, consisting of a morbid and slightly aggressive persuasion of unfaithfulness of his partner, as part of delusional jealousy (Othello syndrome). The remaining neurological examination showed cerebellar dysarthria, xerostomia, right fatiguable ptosis, and axial and segmental ataxia worsened by eye closure. Deep tendon reflexes, initially absent, reversed to normal after repeated tapping.

Electrodiagnostic evaluation, performed at the clinical onset, revealed low-normal amplitudes sensory nerve action potentials (SNAP), normal conduction velocities, small compound muscle action potentials (CMAP) obtained by right median and ulnar nerve stimulation and +500% increase of amplitude after brief muscular exercise.

No decremental response was observed at 3 Hz, while a striking incremental response of +450% was recorded at 50 Hz (see Figures 1 and 2). Serological investigation detected P/Q-type voltage-gated calcium channel (VGCC) antibodies, but not anti-Hu antibodies. Informed consent for cerebrospinal fluid (CSF) examination was not obtained.

Total-body computerized tomography showed a small right retrosternal mass, adjacent to the anterior segment of the superior pulmonary lobe, and hyperplastic lymph nodes in the axillary region bilaterally. Magnetic resonance imaging of the brain was normal. An atypical resection of the right superior lobe via thoracoscopy was performed, followed by several cycles of chemotherapy and radiotherapy. The histological exam showed a LCNEC (see Figures 3 and 4).

Figure 1. Decrement: Destro Abd pollicis brevis. Incremental response to high rates (50Hz) of repetitive nerve stimulation (Right Abductor pollicis brevis).
Administration of prednisone (50 mg on alternate days) caused prompt amelioration of all neurological symptoms, which allowed resumption of work. The psychiatric syndrome progressively disappeared. The good response persisted over two years and no relapses were observed.

Eventually the cancer recurred (paratracheal lymph nodes, liver, and brain metastases) and the neurological picture reappeared with the notable exception of the psychiatric symptoms. The patient died approximately three years after the clinical onset.

**DISCUSSION**

The close association between lung cancer and paraneoplastic diseases is already fully established. Small cell lung cancer (SCLC) is the most prevalent underlying tumour in paraneoplastic disorders, while other lung neoplasias - such as typical carcinoid, adenocarcinoma, squamous cell carcinoma, large cell lung carcinoma and large cell neuroendocrine carcinoma (LCNEC) - are less commonly involved.

Interestingly, the rare LCNEC had been previously described together with LEMS only in two reports in English literature. In both cases the typical Lambert-Eaton clinical presentation of proximal weakness was evident, but signs of encephalitis, such as ataxia or psychiatric manifestations were not described.

Moreover, LCNEC is rarely detected in the so-called anti-Hu syndrome, a disorder characterized by various combinations of paraneoplastic encephalomyelitis, limbic encephalitis, sensory neuropathy/neuronopathy and cerebellar degeneration, associated with high titres of anti-Hu antibodies.

In this regard, among 200 patients with paraneoplastic encephalomyelitis and anti-Hu antibodies, only four cases harboured a LCNEC, and no one of them was diagnosed with LEMS.

To date, LCNEC had never been associated with LEMS and paraneoplastic encephalitis, cerebellar syndrome and ganglionopathy in the same patient.

If paraneoplastic encephalitis is suspected, then, SCLC should be primarily ruled out and levels of anti-Hu antibodies in the serum of patients should be investigated. Every tumour hiding small amount of neuroendocrine cells may show Hu-immunoreactivity, however, Anti-Hu production, indeed, is triggered by an immune response directed towards neuronal antigens ectopically expressed in neuroendocrine tumours, ultimately leading to a cross-reaction with similar antigens present in the nervous system.

Although anti-Hu antibodies may represent a sign of paraneoplastic neurological syndromes, it should be noted that the anti-Hu titres could vary significantly among the different paraneoplastic disorders also in consequence of the immunosuppressive effect of chemotherapy.

**Figure 2.** Low-amplitude CMAP after a single, supramaximal stimulus. Postexercise potentiation of CMAP. Rapid disappearance of postexercise increment.

**Figure 3:** Right superior lobe, hematoxylin and eosin staining, 5X.
Moreover, a few conditions may show low titres or undetectable anti-Hu antibodies, such as SCLC patients without paraneoplastic multifocal neurological disease or with isolated cerebellar degeneration. An extremely low amount of neuroendocrine cells in thoracic and extra-thoracic tumours or an immune mechanism not mediated through Hu-related antigens have been hypothesized in anti-Hu negative patients. In the reported patient harbouring a LCNEC, only the VGCC antibodies, usually present in LEMS, were detected, but not the anti-Hu antibodies.

Large cell neuroendocrine carcinoma is an aggressive neoplasm, which may contain even fewer intracellular neuroendocrine granules. It shares immunohisto-chemical characteristics with neuroendocrine tumours, but morphologic features of large cell carcinomas.

In spite of the absence of antibodies, our patient displayed a clinical presentation resembling the anti-Hu syndrome in addition to Lambert-Eaton confirmed by neurophysiological and serological investigations.

We believe this represents the first case report of LEMS and paraneoplastic multifocal neurological involvement, associated with LCNEC.

It may be argued, however, that ataxia, limbic encephalitis and the prompt response to medical therapy in our patient may evoke the paraneoplastic diseases associated with the brain/testis proteins. Even if we could not test this subject for anti-Ma antibodies, several elements let us reasonably exclude this diagnostic hypothesis.

On a purely clinical basis, the sensory neuropathy and the autonomic dysfunction are not typical features of anti-Ma1, nor of anti-Ma2 syndrome. The serological investigation of 1705 patients with suspected paraneoplastic disorders resulted in the identification of only four cases with anti-Ma1 antibodies, no one having LEMS, and the detected malignancy was never a LCNEC.

As well, Dalmau et al. did not identify any LCNEC among 38 individuals with anti-Ma2 encephalitis. In this report no cases of LEMS were described.

Furthermore, normal neuroimaging distinguishes our patient from antiMa2-associated encephalitis, which usually display MRI brain abnormalities at symptom presentation. It is noteworthy that after starting the therapy with cortisone the patient had a complete recovery from the segmental and axial ataxia, which is common in patients suffering from the antineuropil syndrome, but not in anti-Ma cases.

In conclusion, developing LEMS while suffering from a LCNEC is a rarity by itself, let alone the occurrence of encephalitis, sensory neuropathy and autonomic dysfunction. Such paraneoplastic manifestations - resembling the entity called the anti-Hu syndrome - coexisting with LEMS, may represent an early sign of the large cell neuroendocrine carcinoma of the lung.

REFERENCES