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## Case Report

## Large granular lymphocytic leukemia associated with Lambert–Eaton Myasthenic Syndrome: A case report



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## ABSTRACT

Large granular lymphocytic (LGL) leukemia is an uncommon clonal lymphoproliferative disorder. Lambert–Eaton Myasthenic Syndrome (LEMS) is a rare neuromuscular autoimmune disease caused by pathogenic autoantibodies targeting the voltage-gated calcium channels (VGCC) on the presynaptic nerve terminal. We here describe the case of a 77-year old patient with LGL leukemia, associated with a seropositive and symptomatic LEMS and a seronegative rheumatoid arthritis. LGL leukemia treatment clearly improved LEMS symptoms, and led to anti-VGCC antibodies value decrease. To our knowledge, this is the first ever described association between LGL leukemia and LEMS.

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## 1. Introduction

Large granular lymphocytic (LGL) leukemia is an uncommon clonal lymphoproliferative disorder, which has usually an indolent clinical behavior and can be associated, at diagnosis or during evolution, with a variety of autoimmune disorders including autoimmune cytopenias such as pure red cell aplasia, Sjögrens syndrome and rheumatoid arthritis (RA).<sup>1</sup> Lambert–Eaton Myasthenic Syndrome (LEMS) is a rare neuromuscular autoimmune disease caused by pathogenic autoantibodies targeting the voltage-gated calcium channels (VGCC) on the presynaptic nerve terminal. It traduces by muscular weakness and autonomic dysfunction. It is strongly associated with Lung Small Cell Carcinoma (LSCC), and fulfills the paraneoplastic syndrome definition criteria.<sup>2</sup> We here report on a patient with LGL leukemia, associated with a seropositive and symptomatic LEMS and a seronegative rheumatoid arthritis.

## 2. Observation

A 77 year-old male without any relevant medical history nor professional toxic exposition, presented in 2001 with a permanent

cough (without detectable infectious etiology), proximal muscular weakness, unusual asthenia, and a dry mouth sensation. Clinical examination showed a complete areflexia. Paraclinical explorations showed anti N-type autoantibodies directed against VGCC strongly positives (390 pmol/l; NI < 100), without anti-P/Q type VGCC antibodies. Laboratory tests showed a normal blood cells differential count. Neurophysiological tests showed a trend to lower first compound muscle action potential amplitude, with a discrete post-exercise increment, which were compatible with LEMS. An exhaustive neoplastic screening was performed, showing an asymptomatic and non-capsule disrupting prostatic adenocarcinoma. Patient was effectively treated by hormonotherapy, leading to normalization of PSA-value, but without effect on patient's neurological symptoms. Anti N-type VGCC-directed autoantibodies-value continued to increase (530 pmol l<sup>-1</sup> at maximum). Six months later, patient presented clinical features compatible with active rheumatoid arthritis (RA) (tenosynovitis and arthritis). Laboratory tests showed a moderate hyperlymphocytosis ( $4.6 \times 10^9/l$ ), predominantly composed of LGL. LGL phenotypic expression was CD3+, CD5low, CD7low, CD8+, CD4low, CD16+, CD57+, CD56– and TCRαβ gene rearrangement showed a monoclonal pattern. Patient was neutropenic (PMN:  $0.8 \times 10^9/l$ ). Serum protein electrophoresis did not show hypogammaglobulinemia. C-reactive protein value was below 5 mg/l. Autoantibodies screening showed negativity for Rheumatoid Factor, antikeratin antibodies and antinuclear antibodies, and positivity for antiphospholipid antibody. The patient was treated with steroids (initially 15 mg/day) and methotrexate (7.5 mg/m<sup>2</sup>/week). Clinical manifestations of RA and of neurological symptoms were

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quickly and dramatically improved. This first-line therapy was continued indefinitely, with a steroid-dependence at 6 mg/day regarding rheumatological manifestations, and without any neurological relapse. The patient achieved a complete and persistent hematological response within 10 months. Partial molecular response was documented with a persistence of 10% of clonal TCR $\alpha\beta$  using PCR. The anti-N type autoantibodies against VGCC-value progressively decreased (310 pmol l<sup>-1</sup> at minimum, 11 months after beginning the LGL leukemia treatment; anti-N antibodies assay was never repeated after this date). Neither Lung Small-Cell Carcinoma (LSCC), nor other preexistent carcinoma was detected during the next 9-years follow-up. Finally, the patient died in 2011, 9 years later, at the age of 86 years, due to a brain tumor without any evidence of RA/LGL leukemia nor LEMS relapse.

### 3. Discussion

This observation reports an unusual association of LEMS with LGL leukemia occurring in the same patient, and clearly shows that both diseases benefited from LGL leukemia therapy. Methotrexate and steroids rapidly induced hematological complete remission associated with disappearance of RA and neurological symptoms. Anti-N antibodies titers progressively decreased. Indeed, correlations have already been shown between the anti-N titer evolution and the disease activity in longitudinal studies on single patients.<sup>3</sup>

Moreover, patient did not display any resurgence of LEMS over the time. This observation supports the hypothesis that LEMS could be considered as a paraneoplastic manifestation of LGL leukemia. Since T-regulatory cells protein expression pattern had been shown to be different in some LEMS patients,<sup>4</sup> we can hypothesize that LEMS occurrence could be linked to a specific immunoregulatory system deregulation in the context of LGL leukemia. To our knowledge, this is the first ever described association of LEMS with LGL leukemia, whereas it has been reported in other lymphoproliferative diseases<sup>5</sup> such as multiple myeloma,<sup>6</sup> Hodgkin lymphoma,<sup>7</sup> or even in myeloproliferative ones, such as chronic myeloid leukemia.<sup>8</sup>

About half of the patients presenting with LEMS have a SCLC. For 94% of these patients, LEMS manifestations are usually present 6 months before the SCLC diagnosis.<sup>9</sup> Our patient underwent regular chest CT scan which were always non-contributive. He did not develop any pulmonary symptoms over the 9 years following LEMS diagnosis.

LEMS has been described in association with at least 6 cases of prostatic carcinoma,<sup>2,10–12</sup> which all had some neuroendocrine and/or small cells features. In our patient, histopathology concludes to a localized adenocarcinoma, without any neuroendocrine or small cell feature. Hormonotherapy was efficacious on

the PSA-value, improving neither LEMS manifestations nor anti-N VGCC antibodies values. Anti-N antibodies value even increased. Prostate irradiation was performed with good efficacy on PSA-value, without any impact on the LEMS.

The patient finally died in March 2011 from a cerebral tumor, which had radiological features and quick progression time arguing for its glioblastoma nature. No histological documentation was performed. The long term interval (9 years) between LEMS manifestations and the late onset of brain tumor, suggests that glioblastoma was not linked to LEMS.

LEMS may be difficult to diagnose, and neurological symptoms can be masked or under evaluated in patients having rheumatoid symptoms as it is observed in LGL leukemia. A strict neurological clinical evaluation, completed with systematic electromyography or/and anti-VGCC antibodies assay should be done in this setting. We also suggest that careful examination of blood smears and immunophenotype should be performed for patients having LEMS without evident underlying neoplastic disease.

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