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**Case Report**

# A Rare Case of Lambert-Eaton Myasthenia Syndrome Associated with Non-Hodgkin's Lymphoma: A Case Report and Review of the Literature

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## Keywords

Non-Hodgkin lymphoma · Lambert-Eaton myasthenic syndrome · Peripheral T-cell lymphoma · Autoimmune disorders

## Abstract

***Introduction:*** Lambert-Eaton myasthenia syndrome (LEMS) is a rare autoimmune disorder characterized by autoantibodies targeting presynaptic neuromuscular junctions. It results in muscle weakness and autonomic dysfunction. LEMS can be idiopathic or associated with neoplastic diseases, often small-cell lung cancer. This case report describes a rare instance of paraneoplastic LEMS in a man with non-Hodgkin lymphoma. ***Case Presentation:*** A 57-year-old male with non-Hodgkin lymphoma presented with progressive muscle weakness, diminished reflexes, and autonomic symptoms. Diagnosis revealed LEMS with autoantibodies against voltage-gated calcium channels. Immunosuppressive therapy and lymphoma treatment led to significant improvement in his condition. ***Conclusion:*** This case highlights the rare occurrence of paraneoplastic LEMS in a patient with non-Hodgkin lymphoma. Recognition and timely management of LEMS alongside lymphoma treatment can lead to significant clinical improvement, emphasizing the need for increased awareness of such complex associations.



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## Introduction

Lambert-Eaton myasthenia syndrome (LEMS) is a rare neuromuscular junction transmission disorder primarily characterized by proximal muscle weakness, reduced reflexes, and autonomic symptoms [1]. It is classified as an autoimmune disorder involving the production of autoantibodies targeting voltage-gated calcium channels (VGCCs) at the presynaptic membrane [2, 3]. This immune response leads to a decrease in the levels of acetylcholine available at the neuromuscular junction, contributing to the clinical manifestations of LEMS [4]. LEMS can either be associated with neoplastic conditions, referred to as paraneoplastic LEMS, or it can manifest in the absence of malignancy, known as nonneoplastic LEMS, with the trigger remaining unidentified [5]. The neoplastic form is commonly reported in association with SCLC [5, 6]. In this case report, we present the case of a 57-year-old male diagnosed with non-Hodgkin's lymphoma (NHL) who developed LEMS, an exceedingly rare co-occurrence [7]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534557).

## Case Presentation

A 57-year-old man recently diagnosed with lepromatous leprosy was confirmed with skin biopsy and had been on treatment (rifampicin/clofazimine/dapsone) for 2 months before admission; he was presented to the hospital with complaints of abdominal distension, constipation, vomiting, and a 10-kg weight loss. On examination, the patient was vitally stable. He had evidence of peripheral lymphadenopathy with a distended abdomen and a positive shifting dullness. A computed tomography scan of his abdomen showed mural thickening of the terminal ileum with significantly enlarged mesenteric lymph nodes, mesenteric fat stranding, and intra-abdominal free fluid, suggesting abdominal granulomatous infection or neoplastic process.

Abdominal paracentesis was done and showed atypically large lymphocytes, suggesting high-grade lymphoma, and subsequent flow cytometry showed an abnormal CD4/CD8 double-negative T-cell population (38%) with multiple phenotypic aberrancies. A cervical lymph node biopsy confirmed high-grade peripheral T-cell lymphoma (PTCL), not other specified, a subtype of NHL. A bone marrow examination showed no involvement of T-cell NHL. The patient was staged as a stage IV lymphoma.

He was started on dexamethasone with tumor-lysis syndrome precautions. However, he deteriorated clinically, requiring transfer to the medical intensive care unit (ICU) for severe sepsis. He required antibiotics and antifungals and stayed in ICU care for around 1 week. Once recovered, he was transferred to the national cancer center, where he was commenced on the EPOCH chemotherapy protocol (etoposide, prednisone, vincristine sulfate [oncovin], cyclophosphamide, and doxorubicin hydrochloride [hydroxydaunorubicin]) for six cycles, along with CNS prophylaxis (intrathecal methotrexate). Upon assessment after four cycles, the patient responded well to chemotherapy and attained complete metabolic remission by positron emission tomography/computed tomography. However, his hospital course was complicated by multiple febrile neutropenia episodes and recurrent bacteremia.

During his admission, the neurology team was involved as the patient started to develop generalized weakness without sensory changes and no clear fatigability. On exam, power was decreased in all proximal and distal muscles (3/5), with no other abnormalities. Given the previous history of ICU admission, neurotoxic drug use, and malignancy, the differential diagnosis included critical illness myopathy-neuropathy, toxic neuropathy, and paraneoplastic syndrome.

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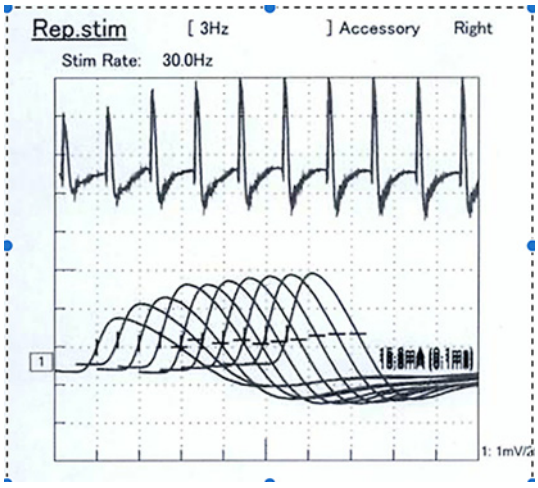


**Fig. 1.** EMG of proximal and distal muscles in the lower and upper limbs. EMG, electromyogram.

Therefore, a complete neurophysiological electromyogram/nerve conduction study was performed. It showed normal distal latencies, normal compound muscle action potential, and normal conduction velocities along with normal F waves in all motor nerves studied. Sensory nerve studies revealed normal onset latencies, normal sensory nerve action potential amplitude, and normal conduction velocities. Needle electromyogram of proximal and distal muscles in the lower and upper limbs exhibited normal insertional activity, no spontaneous activity, and normal motor unit action potential, but with poor recruitment effects. Finally, repetitive nerve stimulation (at 30–40 Hz) showed a significant incremental response (see Fig. 1), suggesting a presynaptic neuromuscular junction disorder (likely LEMS). VGCC antibodies were requested. Unfortunately, it was not done because of technical issues. The patient was started empirically on intravenous immunoglobulins for 5 days as a case of LEMS (as 3, 4-diaminopyridine is not available in our center), which resulted in significant improvement of his motor function. The patient could ambulate afterward, showing a dramatic response to treatment.

The patient was planned for consolidation by autologous bone marrow transplant. Unfortunately, with the recurrent bacteremia and sepsis that accompanied the patient's course due to his immunocompromised state, he was re-admitted to the medical ICU for severe sepsis and multiorgan failure and passed away around 6 months after his initial diagnosis with NHL, despite maintaining a remission status.

## Discussion and Conclusion

PTCL is a rare and aggressive subtype of lymphoma, constituting 5–15% of NHLs in the Western world. It encompasses both peripheral (systemic) and cutaneous forms, originating from T cells and natural killer cells, and often presents at an advanced stage with high International Prognostic Index (IPI) scores. PTCL predominantly affects men and is more common in adults over the age of 60. Diagnosis is challenging, leading to misdiagnosis in at least 10% of cases. Compared to typical diffuse large B-cell lymphoma, most PTCL subtypes have a poor prognosis, with a median overall survival of 1–3 years and a 5-year survival rate of approximately 30% when treated with the standard chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) [8].

Patients with PTCLs have some of the poorest long-term survival rates of blood malignancies, reflecting a decades-long dependence on standard CHOP-based chemotherapies. Patients with T-cell lymphoma may likely relapse after the first treatment in about 75% of cases [9]. Hence, our

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patient was started on the EPOCH protocol, with six cycles and CNS prophylaxis. According to Maeda et al. [10], dose-adjusted EPOCH has a high response rate and may improve outcomes in patients with PTCL. This regimen offers a tolerable toxicity profile, especially in older patients with poor prognoses who may not be candidates for transplantation. EPOCH with dose adjustment may be considered as first-line therapy for PTCL. A recent review (Kim et al. [11]) showed that CHOP with etoposide was correlated with a greater 3-year survival rate than CHOP alone in the frontline treatment of PTCL. At the same time, there was no significant difference in the CR rate. However, numerous innovative agents have been produced recently, including histone deacetylase inhibitors, antifolates, immunomodulatory drugs, nucleoside analogs, and other targeted medicines. Certain novel drugs have the potential to be used with dose-adjusted EPOCH therapy, and their appropriate combination therapies should be found [10, 11].

LEMS is a paraneoplastic or autoimmune illness that affects the neuromuscular junction. More than half of all cases are caused by small-cell carcinoma (SCLC). The most prevalent clinical sign is muscle weakness. Antibodies against VGCCs on presynaptic nerve terminals produce the disease, which causes acetylcholine levels to drop [12]. Non-tumor Lambert-Eaton myasthenic syndrome differs from the paraneoplastic LEMS. Non-tumor Lambert-Eaton myasthenic syndrome appears in the absence of malignancy. An underlying malignancy affects 60% of LEMS patients. SCLC is often associated with LEMS. Other cancers connected to LEMS include non-small-cell and mixed lung carcinomas, prostate cancer, thymoma, and lymphoproliferative disorders [13, 14].

The paraneoplastic manifestations of solid tumors, such as LEMS associated with SCLC, are distinct from the autoimmune manifestations of lymphoid malignancies. Autoimmunity is caused by ectopic expression of neural antigens by tumoral cells (onconeural antigens), and the paraneoplastic presentation usually occurs before cancer is diagnosed. There is also a simultaneous relationship between the activity of the paraneoplastic phenomenon and the tumor. Successful treatment of SCLC frequently results in improved LEMS. In contrast, the disease activity of the paraneoplastic manifestation is often nonsynchronous with that of lymphoid malignancy [15–17]. This can partly be explained because autoimmunity in lymphoma is caused by defective immunological mechanisms rather than molecular mimicry and normal immune systems, as in solid tumors.

Autoimmunity in lymphoid malignancies could be caused by disruptions in anti-idiotype antibody networks or poor regulatory T-cell function. According to the "network theory," natural autoantibodies are generally obscured by anti-idiotypic antibodies [18]. Regulatory T cells play an essential role in maintaining immunologic self-tolerance and, as a result, preventing autoimmunity [19]. Chemotherapy may cause autoimmunity if it causes a decrease in anti-idiotypic antibodies, disrupting anti-idiotypic networks, or a selective depletion of regulatory or suppressor T cells.

Patients with neoplastic diseases other than SCLC have been reported in very few LEMS cases [7, 19–21]. Whichever the underlying cause of LEMS is, it is critical to be aware of it when evaluating weakness in a patient with a lymphoproliferative illness of any age or stage. We propose that any patient with a lymphoproliferative disease who complains of muscle weakness without a clear cause undergo a proper electrophysiological assessment for LEMS using one of the widely known diagnostic modalities before discharge.

## Statement of Ethics

The case was approved by Hamad Medical Corporation Medical Research Center (MRC-04-21-1057) and the patient signed a written informed consent to publish their case (including publication of images). Written informed consent was obtained from the patient's son for the publication of this case report and any accompanying images.

## Conflict of Interest Statement

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

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## Author Contributions

Mohammad Abu-Tineh: manuscript writing and editing, literature review, and final approval. Mohammed A. Alamin: manuscript writing and editing and final approval. Esra'a aljaloudi: manuscript writing and literature review. Awni Alshurafa: manuscript writing, corresponding author, and final approval. Beatriz Garcia-Cañibano: manuscript editing and final approval. Ruba Y. Taha and Sarah A. Elkourashy: manuscript editing, supervision, and final approval.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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