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Myasthenia Gravis and Large Granular Lymphocytic Leukemia: a rare association

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder sometimes observed in hematologic malignancies as a paraneoplastic syndrome. T-cell Large Granular Lymphocytic Leukemia (T-LGLL) is a rare lymphoproliferative clonal frequently associated with autoimmune disorders. Here we report two patients with T-LGLL who developed MG. In both patients the MG was bulbar without generalized weakness and did not involve the thymus. The treatment of T-LGLL led to the resolution of MG symptoms and decrease in acetylcholine receptor antibody titers in both patients suggesting a causative association.

1. Introduction

Large Granular Lymphocytic Leukemia (LGLL) is a rare lymphoproliferative clonal disorder of mature cytotoxic effector memory T-cells or natural killer cells involving blood, bone marrow and spleen. In the majority of cases, it has an indolent clinical behavior and can be associated, at the time of diagnosis or during disease course, with a variety of autoimmune disorders such as rheumatoid arthritis, Sjogren's syndrome and autoimmune cytopenia such as pure red cell aplasia [1].

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies against acetylcholine receptors (AChR) or other functionally related molecules in the postsynaptic membrane at the neuromuscular junction. It presents with fatigable muscle weakness, either generalized or localized [2]. It may be considered a paraneoplastic disorder in some patients since approximately 15% of patients have a thymoma [3]. Conversely, the development of various cancers in patients with MG suggests that this immune disorder may predispose patients to develop malignancies [4].

Here, we report two patients with T-LGLL who developed late-onset MG.

2. Case Presentation

Case 1: An 84-year-old Caucasian man was diagnosed with T-LGLL in 2006. He was initially treated with cyclophosphamide and prednisone for cytopenia in 2007 with a durable hematologic response. However, he developed progressive dysphagia, mild dysarthria, and bilateral ptosis in July 2017, more than ten years after completion of the treatment for T-LGLL. Work-up showed elevated AChR binding antibodies level of 8.35 nmol/L (normal <0.4 nmol/L), AChR blocking antibody with 57% inhibitor (normal <26%), and AChR modulating antibody 88% binding inhibition (normal <45%). No antibodies to the muscle-specific kinase were found. Neither a Tensilon nor EMG was performed. A CT scan of thorax did not show thymoma or an enlarged thymus. Flow cytometry of both peripheral blood and bone marrow showed abnormal T-cell population co-expressing CD3+/CD8+/CD57+/ TCRab+ consistent with the diagnosis of T-LGLL. Clonality studies revealed positive TCR β/γ gene rearrangement. In addition to pyridostigmine 60mg TID, he was placed on prednisone 60mg TID for MG and then transitioned to cyclophosphamide 100 mg QD, with the resolution of his neurological symptoms. Follow-up evaluation in March 2019 revealed persistent low titer of AChR binding antibody level of 0.7 nmol/L, stable hematologic parameters and the absence of neurological symptoms.

Case 2: A 64-year-old Caucasian male with a history of resolved right

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Table 1
Case Reports of MG with T-cell lymphoproliferative disorder

Reference#	Age/ Sex	Lymphoma/ Leukemia Type	Diagnosis of T-LPD	Immunophenotype	Therapy of T-LPD	Response of MG to chemotherapy	Outcome	Neurological Symptoms	Thymus Involvement
6	38/M	Indolent T-LBL	< 1 year after MG	CD1+CD2+CD3+CD4+CD8+	CHOP-bleomycin (vincristine and prednisone omitted) x 3. vincristine, prednisone, methotrexate and asparaginase x 1	yes	CR (lymphoma and MG)	Diplopia, generalized weakness	yes
7	55/M	PTCL-NOS	16 years after MG	CD2+CD3+CD4+CD5+CD7dim+CD8+	CHOP	no	PR (lymphoma, no response of MG)	Ptosis and diplopia	no
9	51/F	T-LBL	1 year after MG	CD1+CD2+CD4+CD5+CD7+	CHOP x 8 cycles	yes	CR (lymphoma and MG)	Facial and limb weakness, ptosis and dysarthria	yes
8	51/F	T-LBL	2-3 months after MG	not specified	CHOP	yes	CR (lymphoma and MG)	Not specified	not specified
10	26/M	T-LBL	9 months before MG	CD3+CD5+CD7+CD10+	IIVP16(ifosfamide, idarubicin, etoposide)	no	Death (palliative care)	Facial and ocular palsy, progressive paraparesis	yes
11	43/M	PRCA/T-ALL	6 years after MG	CD2+CD3+CD5+CD7+CD8+	CHOP x 2 for initial thymoma, then AdVP (adriamycin, vincristine and prednisone) for T-ALL	no	Death from pneumonia/ lymphoma	Easy fatigability and left blepharoptosis	yes
12	59/F	PTCL-NOS	Simultaneous	CD2+CD3+CD5+CD7+CD8+	Chemotherapy (not specified)	no	Death from sepsis	Right eye ptosis, dysphagia, facial weakness	yes
13	81/M	LGLL	Simultaneous	CD3+CD8+CD57+	Prednisone, then Cyclophosphamide	yes	Response (LGLL and MG)	Dyspnea, lower extremity weakness	no
Case 1	84/M	LGLL	11 years after LGLL	CD3+CD8+CD57+	Prednisone, then Cyclophosphamide	yes	CR (LGLL and MG)	Dysphagia, dysarthria, bilateral ptosis	no
Case 2	64/M	LGLL	Simultaneous	CD3+CD8+CD57+	Methotrexate and Prednisone, then cyclophosphamide, then mycophenolate	yes	CR (LGLL and MG)	Dysphagia, dysarthria, and ptosis	no

*Abbreviations: M: male; F: female;T-LPD: T cell lymphoproliferative disorders; T-LBL: T-cell lymphoblastic lymphoma; PTCL-NOS: Peripheral T cell lymphoma, not specified; PRCA: pure red cell aplasia; T-ALL: T-cell acute lymphoblastic leukemia; CHOP: cyclophosphamide, Doxorubicin, Vincristine and prednisone; CR: complete remission; PR: partial remission;

sided Bell's palsy twenty-four years previously, presented with a three-month history of dyspnea on exertion, dysphagia, fatigable dysarthria, and right fatigable ptosis. Initial labs showed severe anemia with a hemoglobin of 6.1g/dL and mild leukopenia. Dyspnea on exertion improved after a blood transfusion. Pulmonary function testing was not done. Peripheral flow cytometry revealed a small population of CD3+/CD57+/TCRab+ T cells. The clonal origin of cells was confirmed with positive TCR β/γ gene rearrangement studies. Subsequent bone marrow biopsy revealed infiltration of marrow with T- LGLL. Neurologic workup showed elevated AChR binding antibody level of 75 nmol/L (normal <0.3 nmol/L) without enlarged thymus on CT. A MRI brain was normal. Tensilon testing and EMGs were not done due to the rapid improvement of symptoms. He was initially treated with methotrexate and then oral cyclophosphamide 100 mg QD and prednisone 40mg QD. Six weeks later, his neurologic symptoms resolved. Three months later, his hemoglobin normalized. He completed six months of therapy with cyclophosphamide and prednisone. Subsequently, he was placed on mycophenolate mofetil per neurology without any recurrence for at least four years. Repeat MG panel testing after five months showed a low titer of AChR binding ab of 3.9 nmol/L, AChR blocking antibody with 37% inhibitors, and AChR modulating antibody 46% binding inhibition.

3. Discussion

Here, we report a case series of patients with MG in the absence of thymoma, which clinically manifested after the diagnosis of LGLL. Recently, Munoz et al reported a similar case, which underlies the significance of LGL proliferation in pathogenesis of Myasthenia Gravis [17]. Handa et al. reported a case of malignant thymoma with clonal thymic T-cell expansion, pure red cell aplasia, polyclonal large granular lymphocytosis and myasthenia gravis [5]. Unlike our case, polyclonal LGL population in peripheral blood did not fulfill the criteria for diagnosis of LGLL, and malignant mixed epithelial-lymphoid type thymoma was more likely the cause for MG.

MG has been reported in association with other T-cell lymphoproliferative disorders such as T-cell lymphoblastic lymphoma and peripheral T cell lymphoma (table 1). In most cases, MG was diagnosed before the malignancy and involved thymus [6-12]. Our cases point to a different mechanism for the development of MG in the LGLL.

T-LGLL can harbor immunologic abnormalities such as seropositivity for rheumatoid arthritis, antinuclear antibody and antineutrophil antibody, polyclonal hypergammaglobulinemia, and circulating immune complexes [13]. Five percent of patients with T-LGLL has B cell dyscrasia, of which monoclonal gammopathy of undetermined significance is most common [14]. Bassan et al. proposed that abnormal LGL population was unable to suppress B-cell activation and immunoglobulin synthesis [15]. In our case, the development of MG after or at the time of diagnosis of T-LGLL supports MG as an immunologic or paraneoplastic manifestation of LGLL. We hypothesize that clonal CD3+/CD8+/CD57+ T-cell LGLL population results in dysregulation of B cells and subsequent development of AChR binding antibody. These autoantibodies were pathogenic and impaired neuromuscular transmission in the postsynaptic membrane through several mechanisms such as complement-mediated injury and removal of AChR from the muscle membranes, cross-linkage of divalent AChR autoantibodies that result in internalization of AChR, or direct blockade of AChR by the autoantibodies [16]. The complete resolution of MG symptoms and a significant decrease in AChR abs after LGLL treatment further support causal relationship between these two rare disorders. Interestingly, in both patients, MG was bulbar without generalized weakness, which is less common in late-onset MG [2].

4. Conclusions

Two patients with T-cell LGLL and MG without thymic involvement were described here. In both cases, the complete resolution of MG symptoms and a significant decrease in AChR titers after T-LGLL treatment suggests a causal relationship. We hypothesize that T-LGLL leads to B cell dysregulation and production of AChR autoantibodies in both cases.

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