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# Myasthenia gravis as an unusual non-hematological autoimmune manifestation of a relapsed chronic lymphocytic leukemia – clinical case and review of literature

S. DIMITROVA, M. EFRAIM, I. MICHEVA

Department of Hematology, Medical University, UMHAT "Sveta Marina", Varna, Bulgaria

**Abstract. – BACKGROUND: Autoimmune phenomena are well known to complicate chronic lymphocytic leukemia (CLL) and occur in 10% to 25% of the cases. Although less common, non-hematological autoimmune manifestations have been reported. Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, characterized by fatigable weakness of the extraocular, bulbar, and limb musculature. The co-existence of MG and CLL is exceedingly rare and there are very few cases reported in literature.**

**CASE PRESENTATION: We present a case of a 63-year-old female patient with a severe form of MG which is likely related to a relapse of CLL. Treatment with combined targeted and immunotherapy was initiated with acceptable tolerability.**

**CONCLUSIONS: Targeted agents and monoclonal antibodies exert complex activities on the patient's immune system. It will be of interest to assess their role in managing autoimmune complications, accompanying CLL.**

*Key Words:*

*Myasthenia gravis, Chronic lymphocytic leukemia, Acetylcholine receptor antibodies (AchR), autoimmune hemolytic anemia (AIHA), Autoimmune cytopenias (AIC), B cells.*

## Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults, resulting from clonal expansion of B cells in blood, marrow, and secondary lymphoid tissues[1]. Autoimmune phenomena are well known to complicate CLL and occur in 10% to 25% of the cases[2,3]. These are predominantly autoimmune cytopenias (AIC) that affect 4-7% of CLL patients and mainly consist of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia[4]. Although less common, non-hematological autoimmune manifestations have also been determined[2,5,6]. The most frequent ones are cases of bullous pemphigus, Hashimoto's thyroiditis, rheumatoid arthritis, vasculitis, and acquired angioedema, but cases of autoimmune disorders that are extremely rare in the general population have also been reported[4].

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, characterized by fatigable weakness of the extraocular, bulbar, and limb musculature. This condition is mediated by acetylcholine receptor (AchR) antibodies in 80-90% of patients[7]. MG is a well-recognized paraneoplastic phenomenon of a thymoma in approximately 15% of patients[8]. The diagnosis of MG and an extrathymic malignancy is exceedingly rare. There are very few cases of concurrent MG and CLL reported (up to 14 cases), with simultaneous (within 1 month) diagnosis identified in 6 of them[9-11].

We present a case of a patient with a manifestation of a severe form of MG which is likely related to a relapse of CLL.

## Case Presentation

Our patient is a 63-year-old female, who was diagnosed with CLL (Binet clinical stage A) in 2011. She was under observation till 2016 when she already fulfilled the "need to treat" criteria, representing with disease-related symptoms and progressive lymphocytosis. Immuno-chemotherapy according to RFC protocol (Rituximab was administered on day 1 at 375 mg/m² for course 1 and 500 mg/m² for courses 2-6, Fludarabine - 25 mg/m² and cyclophosphamide 250 mg/m² on days 2-4 for course 1 and days 1-3 for courses 2-6) was initialed and 5 cycles were accomplished. The 6th cycle was omitted due to persistent bone marrow suppression and prolonged cytopenias. Nevertheless, clinical remission was achieved. At that time,

*Corresponding Author:* Dimitrova S. MD; e-mail: stelladimitrova@abv.bg

she presented with several comorbidities, arterial hypertension, diabetes type II and Hashimoto's thyroiditis with hypo function (L-thyroxin supplementation).

In 2019 the patient was hospitalized in intensive care unit with complains of progressive muscle weakness, diplopia, ptosis first of the right eyelid and secondly of the left one. All the symptoms she developed in a period of one week. She complained of difficulties in chewing and swallowing and developed dysphonia. According to the clinical presentation and the rapid evolution of the neurological symptoms the diagnosis of MG pseudoparalitica was assumed. From the somatic physical examination, no lymphadenopathy or hepato-splenomegaly was found. The neurological status revealed bilateral ptosis, dysphonia, dysphagia, and proximal pathological muscle weakness of all extremities. Laboratory results showed normal complete blood count (CBC), electrolytes, creatinine, urea, calcium, phosphate, magnesium, creatine kinase, C-reactive protein, hemoglobin A1c, vitamin B12 serum level and thyroid hormones. CT of the chest and abdomen was negative for thymoma and/or lymphadenomegaly and hepato-splenomegaly. During the hospitalization she developed progressive dysphagia and acute respiratory failure which leaded to intubation and consecutive tracheostomy. After discharge from the hospital, she was left on treatment with Kalymin 4x60 mg/daily.

In May 2022 the patient was hospitalized in the Clinic of Hematology with complains of fatigue, hemorrhagic rash, and profuse night sweats. The physical examination revealed slightly pale skin and conjunctiva, generalized lymphadenopathy of cervical, axillary, and inguinal lymph nodes of approximately 2 cm in diameter and no signs of abdominal organomegaly. The blood picture counts revealed extreme leukocytosis with absolute lymphocytosis and anemia and thrombocytopenia (Figure 1). The biochemical analysis showed creatinine, 84 mcmol/L (range 44-97 mcmol/L); lactate dehydrogenase, 545 U/L (range 208-378 U/L); total bilirubin, 11 mcmol/L (5-21 mcmol/L); direct bilirubin, 3.4 mcmol/L (range 0-3 mcmol/L); β 2 microglobulin, 5.6 mg/L (range 0,6-2,4 mg/L); vitamin B12, 478 pmol/L (range 156-672 pmol/L). The immunohematology showed auto- and alloantibodies in all temperature regimens and positive indirect (++) and direct Coombs test (++++) with no definitive clinical and biochemical signs of hemolysis. CT of chest and abdomen revealed generalized lymphadenopathy in areas above and below the diaphragm (axillary, hilus of the lung, pretracheal, mediastinal, mesenteric, paraaortic, inguinal) with maximum size 27/10 cm in diameter and slightly enlarged spleen 120/60 mm. The fluorescence *in situ* hybridization (FISH) analysis for del(17)(p13) was negative. Treatment according to the Rituximab/Venetoclax protocol (Titration Phase (Week 1 to 5), Venetoclax 20 mg/daily PO

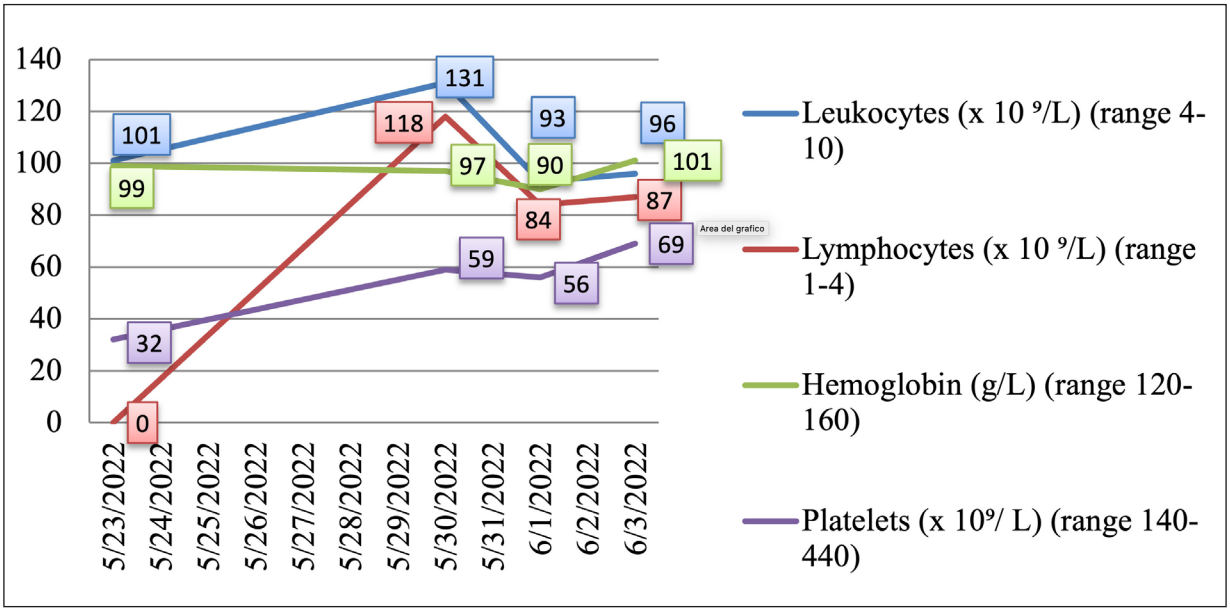


**Figure 1.** Linear chart, representing consecutive counts of leucocytes, lymphocytes, hemoglobin and platelets in the disease course.

in week 1; 50 mg/daily PO in week 2; 100 mg/daily PO in week 3; 200 mg/ daily PO in week 4 and 400 mg/daily PO in week 5; Cycle 1 (Week 6 to 9), Venetoclax 400 mg/daily PO from day 1 to 28 and Rituximab 375 mg/m$^2$ in day 1) was initiated. The patient accomplished the first course of the regimen with no signs of tumor lysis syndrome or other toxicity and achieved hematological response.

## Discussion

Different studies[4] described the occurrence of non-hematological autoimmune events in patients with CLL. Even though there is no strong evidence of a clear predisposition to autoimmunity in CLL patients, the association between CLL and non-hematological autoimmune phenomena is undeniable and is also supported by the described frequent co-occurrence of CLL progression and autoimmune disorder flares[12]. On the contrary, a predisposition to develop CLL in patients with underlying autoimmune disease was not confirmed in two different population-based studies[13,14].

MG is a B cell mediated disease targeting the postsynaptic membrane of the neuromuscular junction, resulting in impaired neuromuscular transmission and fewer functional AchR-s. AchR antibodies are polyclonal IgG antibodies, generated in part by a T cell dependent B cell response[15,16]. Similarly, T helper cell dysfunction and pathological antigen presentation have been shown to contribute to polyclonal IgG antibody production in CLL[17].

It has also been suggested that abnormal regulatory T (T-reg) cells participate in the pathogenesis of autoantibody formation in CLL, due to impaired peripheral tolerance[17]. Similar to autoantibody formation in CLL, dysfunctional T-reg cells play a critical role in Ach-R antibody formation in MG[18].

Another hypothesis confirming similarity in the pathogenesis of CLL and MG is that they both are characterized by deleterious B cell production and regulation, involving especially B cell-activating factor (BAFF). BAFF is a member of the tumor necrosis factor ligand family that promotes B cell maturation and survival. When over-expressed, BAFF prevents B cell apoptosis, thus contributing to malignancy and autoimmunity. In general, auto-reactive antibodies rely more heavily on BAFF for survival, therefore excess BAFF selectively promotes the accumulation of these antibodies[19]. In patients with MG, serum BAFF levels are significantly higher compared to non-myasthenic controls; moreover, AchR antibody-positive patients tend to have higher BAFF levels than seronegative ones[20]. BAFF has been identified as a key player in malignant B cell development and maintenance in CLL. CLL cells express receptors for BAFF and may even express BAFF in an autocrine fashion to promote cell survival[21].

A matter of discussion in the particular clinical case is the possible concomitant drug-induced mechanism of autoimmune complication. CLL directed drugs have been reported to trigger AIC, although the mechanisms underlining this phenomenon are not completely understood. For instance, prospective and retrospective studies of CLL patients treated with single agent Fludarabine reported a significant incidence of AIHA, ranging from 11% to 23%[22]. Non-hematological autoimmunity related to chemotherapy is a rare event and only sporadic cases have been reported, all in association with purine analogues-based regimens. Skin manifestations, such as erythema anulare, vasculitis, pemphigus, and toxic epidermal necrolysis have been described, as well as p-ANCA positive glomerulonephritis[23,24].

## Conclusions

Non-hematological autoimmune complications in CLL patients are less frequent and encompass a wide range of different clinical disorders and conditions. In the era of targeted agents (BTK-inhibitors, BCL-2 inhibitors, etc.) and new multipotent combinations (including different generations of anti-CD20 monoclonal antibodies) for the treatment of CLL, it will be of interest to assess their role especially in autoimmune complications, considering both their therapeutic function and/or possible influence in inducing autoimmune phenomena. These molecules exert complex activities on the patient's immune system, which may eventually be responsible for either the management or the trigger of autoimmune complications.

### Conflict of Interest

Nothing to declare.

### Informed Consent

The subject was informed about the study, and provided informed consent.

### Authors' Contribution

Material preparation, data collection and analysis were performed by Dimitrova S. and Efraim M. Analysis and interpretation of data were performed by Dimitrova S. Supervision of the report was done by Micheva I. The manuscript was written by Dimitrova S. and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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### ORCID ID

Dimitrova S: 0000-0001-8074-2271
Micheva I: 0000-0003-2641-8635
Efraim M: 0000-0001-6570-6643

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