

CASE REPORT

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Uncommon cause of lymphocytosis: Case report of lymphocytosis secondary to lithium usage

Deniz Donmez, Meral Ilgaz, Ümit Yavuz Malkan

ABSTRACT

Lithium, which is widely used in mood disorders, has several side effects. Lymphocytosis is a rare side effect. The patient was a young man in his twenties. The patient referred from psychiatry for persistent lymphocytosis. After the initial evaluation, the possible relationship between lithium and lymphocyte levels was considered. The diagnosis of lymphocytosis secondary to lithium intake can only be made with the elimination of other possible causes of lymphocytosis. Therefore, possible viral infections, possible drug interactions, possible systemic diseases, and malignancies were evaluated and eliminated. After evaluation, a correlation was found between lithium blood level and lymphocyte count. The patient started to be followed up.

Keywords: Leukemia, Leukocytosis, Lithium, Lymphocytosis

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INTRODUCTION

Differential diagnosis of the leucocytosis, more specifically differential diagnosis of the lymphocytosis secondary to lithium usage, is important because hematologic malignancies may also cause lymphocytosis and quick intervention is essential for hematologic malignancies [1]. Knowledge about the incidence of lithium associated lymphocytosis among lithium using patients are limited but there are some studies showed that among a group consisted of 33 patients, leukocytosis occurred in 13 cases (39%), of which 6 cases (18%) was of transient form, 5 cases (15%) of persistent form, and 2 cases (6%) of unknown type [2]. During toxicity, the incidence can increase up to 85.7% [3]. Lithium often increases white blood cell counts but at the same time reduces blood lymphocyte counts causing lymphopenia, but also lithium stimulates mitogenic response of human lymphocytes in vitro [4, 5]. In this case report, we will describe the differential diagnostic approach for leukocytosis and lymphocytosis in a patient using lithium.

CASE REPORT

A 26-year-old Caucasian male patient, who had bipolar disease and hypothyroidism and was treated with valproic acid, lamotrigine, lithium, and levothyroxine (25 mcg) and had lymphocyte higher than $4 \times 10^3/\mu\text{L}$ for six months, was referred to hematology for leucocytosis etiology investigation. Body temperature was 36° , blood pressure was 130/85 mmHg, pulse was 85 per minute, and respiratory rate was 16 per minute. He came from a middle-class family with no history of hematological disease. During the referral he had no B symptoms. Hepatosplenomegaly or superficial lymphadenopathy was absent. In systemic evaluation, no infection focus was detected. Complete blood count, cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein–Barr virus (EBV) serologies, thyroid stimulating hormone

(TSH), creatinine, albumin, lactate dehydrogenase (LDH), peripheral blood smear, and anteroposterior chest X-ray were requested. Chest X-ray showed no mediastinal, hilum enlargement, or another potential lymphadenopathy. Total white cell count was $13.5 \times 10^3/\mu\text{L}$. Hemoglobin (15.3 g/dL) and trombocyte counts ($337 \times 10^3/\mu\text{L}$) were within the normal range. Mature lymphocytes with no smudge cells or with no blasts were detected in the peripheral blood smear (Figure 1). Immunoglobulin G (IgG) antibodies were detected for CMV and EBV. Anti-HB antibodies were detected secondary to the vaccination and other serology tests resulted negative. Lactate dehydrogenase (111 U/L), creatinine (0.74 mg/dL), and albumin (4.72 g/dL) were within the normal range and TSH was within the lower half of the normal range. After these initial tests abdominal, axillary, inguinal, and neck ultrasonography were requested for possible lymphadenopathy. T cell receptor (TCR) and B cell receptor (BCR) clonality gene rearrangement polymerase chain reaction (PCR) and chronic lymphocytic leukemia (CLL) flow cytometry were requested from peripheral blood. T cell receptor and B cell receptor clonality was not detected. CD200, CD25, and CD23 were found negative and CD20 and CD5 were found within the normal range (Table 1). During the follow-up, valproic acid levels have remained stable and blood lithium levels have been converted into a graphic to compare with the lymphocyte count (Figure 2). Lamotrigine dose started as 75 mg at July 2022 and gradually increased to the 200 mg within four months. During the follow-up, valproic acid dose has remained same at 2000 mg. The patient was taking 2×450 mg lithium at the beginning of July 2022. After this date dose was reduced to the 1×450 mg. During the interim period, the dosage was continued at 1×450 mg, and later it was increased back to 2×450 mg in July 2023. Even though correlation between the blood lithium level and lymphocyte count did not match perfectly, after possible malignancies were excluded, considering the patient’s drug history, it was decided that lithium was the only drug that had the potential to cause leukocytosis and lymphocytosis, which could cause the patient’s current condition. The patient began to be monitored with a complete blood count and peripheral blood smear.

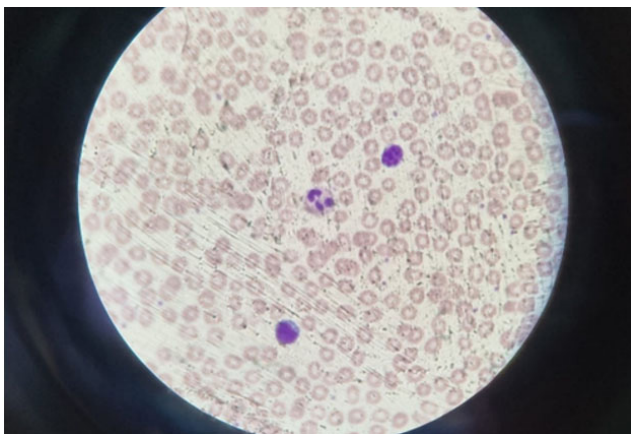


Figure 1: Peripheral smear showing mature cells (Wright’s stain).

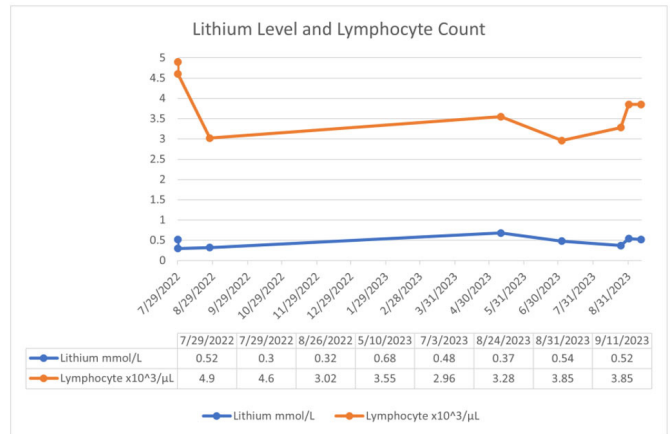


Figure 2: Lithium level and lymphocyte count.

Table 1: CLL flow cytometry from peripheral blood (CD: cluster of differentiation)

Living cell count	67%
CD 3 count	72%
CD4 count	39%
CD5 count	72%
CD5/19 count	–
CD8 count	31%
CD10 (CALLA)	–
CD11c count	–
CD16 count	–
CD19 count	9%
CD20 count	9%
CD22 count	–
CD23 count	–
CD25 count	–
CD38 count	–
CD43 count	–
CD45 count	20%
CD49d count	–
CD56 count	44%
CD57 count	–
CD79b count	–
CD95 count	–
CD103 count	–
CD123 count	–
CD200 count	–
Kappa	53%
Lambda	34%
FMC7	–

DISCUSSION

Lithium is a mood regulator which is widely used in manic depressive patients. Cardiac arrhythmia, ataxia, sleeping disorders, memory impairment, acne vulgaris, dyspepsia, hypercalcemia, hypothyroidism, and nephrogenic diabetes insipidus are the most common side effects of lithium. However, even though it is rare there are case reports that support correlation between lithium blood levels and lymphocyte count [5, 6]. There is a follow-up study that had found no correlation between the lithium blood levels and lymphocyte counts but also showed that lithium users had higher lymphocyte counts [7].

Even though lithium primarily increases the leucocyte count and neutrophil percentage and reduces the percentage of the lymphocyte it also increases the lymphocyte count [2]. For the evaluation of the lymphocytosis, potential infectious causes were eliminated by comprehensive physical examination, food consumption, history, and viral serology studies [8]. B symptoms were questioned. Drug interactions were evaluated. Drugs that he has been using are mostly associated with lymphopenia, but among them lithium was associated with lymphocytosis [7]. The peripheral blood smear evaluated for hematologic malignancies [1]. Even though CLL was not among the suspected diagnosis it should have been eliminated. T cell receptor and B cell receptor gene rearrangement and CLL flow tests were performed to eliminate potential hematologic malignancies [8]. Bone marrow biopsy was not performed because the patient's hemoglobin and trombocyte counts were normal. The patient's lymphocyte count slightly correlated with the blood lithium level [2, 7, 9]. After the initial evaluation, the patient was followed up monthly with the psychiatry. During controls, blood count, peripheral smear, and physical examination (for lymphadenopathy and hepatosplenomagaly) were requested.

CONCLUSION

Lithium is an overlooked and a forgotten cause of lymphocytosis. Before 2000s there have been case reports about lithium and its hematologic side effects. Even though hematologic side effects are rare, especially lymphocytosis, due to lithium's wide usage, clinicians may encounter cases such as our's. All patients should be systemically and thoroughly evaluated. All possible causes should be eliminated by minimally invasive and cost-effective methods.

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Author Contributions

Deniz Donmez – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Meral Ilgaz – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ümit Yavuz Malkan – Conception of the work, Design of the work, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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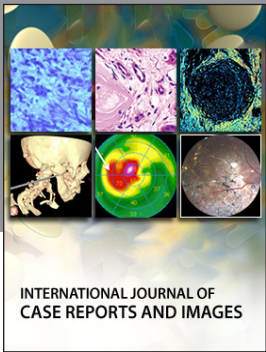
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