DOI: 10.4274/jmsr.galenos.2025.2024-11-2

J Mult Scler Res

CASE REPORT

Systemic Lupus Erythematosus and Secondary Sjögren's Syndrome Following Treatment with Alemtuzumab for Multiple Sclerosis: Case Report

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Abstract

Alemtuzumab, a humanized monoclonal antibody that targets CD52, is a potent treatment for relapsing-remitting multiple sclerosis (RRMS). Despite its efficacy, alemtuzumab can trigger secondary autoimmune disorders, which most commonly involve the thyroid and hematologic systems. Herein, we have presented the case of a 36-year-old woman with highly active RRMS who developed a rare presentation of systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (sSS) 42 months after her last alemtuzumab infusion. While cases of SLE following alemtuzumab administration are extremely rare, the development of Sjögren's syndrome (SS) in this context is previously unreported. The patient exhibited pancytopenia, proteinuria, autoimmune marker positivity (anti-nuclear, anti-double stranded DNA, anti-Sjögren's syndrome type A), and low complement levels. leading to the SLE and sSS diagnoses and treated with corticosteroids, hydroxychloroquine, mycophenolate mofetil, and tacrolimus. This case underscores the importance of monitoring alemtuzumab-treated patients for delayed autoimmune complications and highlights the potential role of B and T cell dysregulation in secondary autoimmunity. Further research is necessary to elucidate the mechanisms underlying these rare adverse events.

Keywords: Alemtuzumab, anti-CD52 therapy, systemic lupus erythematosus, Sjögren's syndrome, secondary autoimmunity, adverse events

Introduction

Alemtuzumab is a highly effective humanized monoclonal antibody that targets the cell surface protein CD52. It is widely recognized and utilized as a powerful disease-modifying treatment in patients with active relapsing-remitting multiple sclerosis (RRMS) (1). Patients with RRMS undergoing treated with alemtuzumab may experience some side effects such as infusion-associated reactions, infections, and secondary autoimmune disorders involving the thyroid gland and hematologic system. Besides thyroid and hematological disorders, other secondary autoimmune disorders are rare (2,3).

Herein, we have presented a rare case of systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (sSS) that developed 42 months after a patient with highly active RRMS was treated with alemtuzumab. Only one other case of post-alemtuzumab infusion SLE has been reported in the literature (4). However Sjögren's syndrome (SS, alone or in conjunction with other autoimmune diseases, has not been reported. This case report highlights the potential for further understanding and managing the adverse effects of alemtuzumab treatment.

Case Report

A 36-year-old female was diagnosed with RRMS in 2013, at the age of 25, after she had complained of imbalance. Disease-modifying therapy was initiated with glatiramer acetate (GA) (20 mg/daily). In 2014, GA was escalated to fingolimod because of persistent clinical and radiological

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Received: 19.12.2024 **Accepted:** 20.01.2025 **Epub:** 18.03.2025

Cite this article as: Demir S, Gungor Dogan I, Kutlug Agackiran S, Tasdelen B, Cetinkaya Tezer D. Systemic lupus erythematosus and secondary sjogren syndrome following treatment with alemtuzumab for multiple sclerosis: case report. J Mult Scler Res.

disease activity. In 2019, a severe multisymptomatic attack was treated with intravenous high-dose methylprednisolone and a series of plasma exchanges. After fingolimod therapy failed, alemtuzumab was administered in December 2019. A second cycle of alemtuzumab therapy was initiated in December 2020. After initiation of alemtuzumab therapy, no further clinical or radiological disease activity was observed.

Forty-two months after the last alemtuzumab infusion, the patient presented to our neuroimmunology clinic with complaints of widespread body pain and swelling of the hand and foot that had gradually worsened over the past 4 weeks. Although the patient's neurological condition appeared both clinically and radiologically stable, she was diagnosed with pancytopenia (white blood cell count, $2.92x10^3$/uL; hemoglobin level, 7.4 g/dL; and platelet count, 50×10^3/uL) and proteinuria (1.025 g/24h). The nutritional parameters were within the normal range, and the peripheral blood smear did not reveal any abnormality. Further tests yielded the following results: positive anti-nuclear antibody titer of +3, anti-double stranded DNA antibodies level of 718.23 IU/mL (reference value <100 IU/mL), anti-Sjögren's syndrome type A positivity, low complement levels (C3: 0.32 g/L, reference value 0.9-1.80; C4: 0.03 g/L, reference value 0.1-0.4), and direct and indirect Coombs positivity without overt hemolysis. Creatinine values ranged from 0.9 to 1.23 mg/dL (reference value 0.5-0.9) during follow-up, and no casts or dysmorphic erythrocytes were observed in the urinary sediment. The Schirmer test yielded a positive result, with 2 mm of wetting in each eye. Furthermore, imaging revealed the presence of pericardial and pleural effusion.

Based on the available data, the patient was diagnosed with SLE with sSS. The patient was promptly treated with intravenous methylprednisolone (250 mg for three consecutive days), followed by oral corticosteroids, hydroxychloroquine (5 mg/kg), and mycophenolate mofetil (2*500 mg/daily) for remission induction. Because the patient was underweight, lower doses of the drugs were preferred. Due to the presence of thrombocytopenia, a renal biopsy was not feasible. In the first month of the treatment, the proteinuria level reached the nephrotic range while the corticosteroid doses were tapered. As a result of the insufficient renal response, tacrolimus (1 mg/daily) was added to the treatment regimen.

Discussion

Alemtuzumab targets CD52, a protein found in abundance on the surface of T- and B-lymphocytes and in lower concentration on the surface of natural killer cells and other cell. It causes a rapid and significant decrease in the number of peripheral lymphocytes via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytolysis, and apoptosis (5). Subsequently, T- and B-lymphocytes repopulate in the periphery at distinctive speeds across different subsets, significantly rebalancing the immune system (6). The cause for the emergence of secondary autoimmunity after treatment with alemtuzumab remains unclear. However, it has been attributed to unexpected off-target effects as a result of imbalances among the different cell subsets during immune cell repopulation. In particular, the recovery of B-cells in the context of a delayed recovery of regulatory T-cells may account for the secondary B-cell autoimmunity (7,8). Furthermore, incomplete T-cell repertoire renewal and homeostatic clonal T-cell expansion can contribute to an autoimmune state (9,10). In this context, both antibody-mediated and T-cell-mediated autoimmune diseases have been described in the literature following treatment with alemtuzumab (4,11).

Understanding the immune system's response to treatments is crucial. Our patient, who had an 11-year duration of highly active RRMS, was sequentially administered GA, fingolimod, and alemtuzumab. She developed a rare case of secondary autoimmunity (SLE and sSS) 42 months after the last alemtuzumab infusion. Because they are closely related to chronic inflammatory clinical conditions of autoimmune nature, the incidence of sSS in patients with SLE can reach up to 19.5% (12,13). This case report not only sheds light on secondary autoimmune disorders caused by alemtuzumab but also provides evidence of the strong immune connection between SLE and SS, particularly in terms of B cell immunity, and an abnormal T cell response even appeared as secondary immunity.

Conclusion

In conclusion, thorough research is crucial to enhance our knowledge of B-cell colonization and T-cell repertoire in relation to secondary immunity. Furthermore, patients being administered alemtuzumab should be closely monitored for the development of various autoimmune conditions. This responsibility is crucial to minimize the risk of delayed diagnosis and treatment.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.G.D., S.K.A., Concept: I.G.D., S.K.A., D.C.T., Design: S.D., Data Collection or Processing: I.G.D., S.D., Analysis or Interpretation: I.G.D., S.K.A., Literature Search: I.G.D., B.T., Writing: I.G.D., B.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Patient consent for publication: Written informed consent was obtained from the patient.

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