International Journal of Medical Science and Pharmaceutical Research

ISSN(e): 3050-5720
ISSN(p): 3050-5712

Vol. 3 (4): 171-175, April 2026

Home Page: https://ijmspr.org/

Quadruple Autoimmune Syndrome: Sjögren's Syndrome, Systemic Lupus Erythematosus, Systemic Sclerosis, and Celiac Disease

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KEYWORDS:

Multiple autoimmune syndrome; Sjögren's syndrome; systemic lupus erythematosus; systemic sclerosis; celiac disease; overlap syndrome; autoimmunity

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DOI: 10.55677/IJMSPR/2026-3050-I412

Published: April 25, 2026

ABSTRACT

Multiple autoimmune syndrome (MAS) is characterized by the coexistence of three or more autoimmune diseases in a single patient and reflects a profound breakdown of immune tolerance. Although overlap syndromes are relatively common in rheumatology, the occurrence of four distinct autoimmune diseases remains exceptionally rare. We report the case of a 40-year-old woman who sequentially developed primary Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and celiac disease over a prolonged follow-up period. The initial presentation was marked by cytopenias, positive antinuclear antibodies, anti-Ro/SSA positivity, and glandular dysfunction, leading to the diagnosis of Sjögren's syndrome. Subsequently, the patient evolved with cutaneous involvement, hypocomplementemia, and systemic features fulfilling classification criteria for systemic lupus erythematosus despite persistently negative anti-dsDNA antibodies. Years later, she developed Raynaud's phenomenon, esophageal dysmotility, interstitial lung disease, and skin fibrosis, consistent with systemic sclerosis. Concomitantly, gastrointestinal manifestations led to the diagnosis of celiac disease confirmed by histopathology. The patient required multiple immunosuppressive therapies, including methotrexate, azathioprine, and mycophenolate mofetil, achieving clinical stabilization after a severe episode of pericardial effusion. This case highlights the dynamic evolution of autoimmunity, the heterogeneity of serological profiles, and the importance of long-term surveillance in patients with autoimmune diseases. It also reinforces the role of shared genetic and immunological mechanisms underlying multiple autoimmune conditions.

Cite the Article: *Carvalho, J.F. (2026). Quadruple Autoimmune Syndrome: Sjögren's Syndrome, Systemic Lupus Erythematosus, Systemic Sclerosis, and Celiac Disease. International Journal of Medical Science and Pharmaceutical Research, 3(4), 171-175. https://doi.org/10.55677/IJMSPR/2026-3050-I412*

INTRODUCTION

The coexistence of two or more autoimmune diseases in a single patient is defined as an overlap syndrome and occurs in a significant proportion of individuals with immune- mediated disorders, particularly within rheumatology [1]. Among these associations, primary Sjögren's syndrome is frequently observed in combination with other systemic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [2]. The occurrence of three or more autoimmune diseases characterizes multiple autoimmune syndrome, a condition first described in 1988, which reflects a broader breakdown of immunological tolerance and shared pathogenic pathways [3]. Cases involving four distinct autoimmune diseases are exceptionally rare and remain poorly described in the literature. The present report describes a patient who sequentially developed primary Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and celiac disease, highlighting the dynamic evolution of autoimmunity and the complexity of diagnosis and management in such scenarios.

CASE REPORT

A 40-year-old female patient with a 10-year history of unexplained leukopenia was referred for rheumatologic evaluation in June 2014. She had a family history of systemic lupus erythematosus. At presentation, physical examination was unremarkable. Laboratory investigation revealed mild anemia, leukopenia with lymphopenia, and thrombocytopenia, along with a high-titer antinuclear antibody (ANA 1:640), positive anti-Ro/SSA antibodies, elevated rheumatoid factor, and hypocomplementemia with reduced C3 and markedly decreased C4 levels. Other autoantibodies, including anti-dsDNA, anti-Sm, anti-RNP, anti- La/SSB, anti-CCP, and ANCA, were negative. Objective evaluation of glandular function demonstrated severe keratoconjunctivitis sicca with a Schirmer test of 1 mm/5 minutes and significant staining on Rose Bengal test, in addition to reduced salivary gland function on scintigraphy. Infectious causes were excluded. Based on these findings, the patient fulfilled classification criteria for primary Sjögren's syndrome according to established international criteria [4], and treatment with hydroxychloroquine was initiated, with subsequent clinical and laboratory improvement.

Approximately one year later, the patient developed persistent cutaneous lesions on the upper limb, initially unresponsive to dermatological treatment. Histopathological evaluation suggested an autoimmune etiology. Over the following months, she presented with malar rash, worsening cytopenias, and persistent hypocomplementemia. Although anti-dsDNA and anti-Sm antibodies remained negative, the combination of clinical manifestations, ANA positivity, and complement consumption allowed the classification of systemic lupus erythematosus according to SLICC criteria [5]. Immunosuppressive therapy was initiated with methotrexate, azathioprine, and corticosteroids, resulting in clinical remission. During follow-up, she developed transient elevation of liver enzymes attributed to methotrexate, requiring dose adjustment, while maintaining disease control.

In the subsequent years, the patient remained clinically stable, although persistently low C4 levels were noted. In 2021, she developed pleuritic chest pain, and imaging studies revealed interstitial lung involvement and a small pericardial effusion. Concomitantly, she reported progressive gastroesophageal reflux symptoms. Physical examination showed a scleroderma facies and thickness of the hands. (see Figures 1 and 2). Esophageal manometry demonstrated distal aperistalsis and hypotonia of the lower esophageal sphincter, and pH monitoring confirmed pathological reflux. In 2022, she developed Raynaud's phenomenon, digital skin thickening, and microstomia. Nailfold capillaroscopy showed microvascular abnormalities, and skin biopsy confirmed scleroderma. Chest computed tomography demonstrated interstitial lung disease and esophageal dilation. Based on clinical, functional, and imaging findings, she fulfilled classification criteria for systemic sclerosis, limited cutaneous form [6]. Immunosuppressive therapy was optimized with methotrexate and later switched to mycophenolate mofetil due to disease progression and pericardial involvement.

During the same period, the patient developed gastrointestinal symptoms including dyspepsia and intolerance to certain foods. Upper gastrointestinal endoscopy with biopsy demonstrated histological findings compatible with celiac disease, establishing the diagnosis in association with her autoimmune background [7]. A gluten-free diet was recommended, with clinical improvement.

In early 2024, she presented with a large pericardial effusion requiring surgical drainage. Following intervention and escalation of immunosuppressive therapy, including mycophenolate mofetil and corticosteroids, she achieved clinical stability. At the most recent follow-up, the patient remains asymptomatic under treatment with hydroxychloroquine, mycophenolate mofetil, vasodilators, and supportive therapy, with stable laboratory parameters.

DISCUSSION

The present case illustrates a rare and complex example of multiple autoimmune syndrome involving four distinct autoimmune diseases. The sequential development of primary Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and celiac disease reinforces the concept of shared pathogenic mechanisms underlying autoimmunity. Genetic susceptibility, particularly involving HLA class II alleles, has been implicated in the predisposition to multiple autoimmune diseases, suggesting a common immunogenetic background [8]. Environmental factors, including infections and hormonal influences, may further contribute to disease expression in genetically predisposed individuals.

From an immunological perspective, these diseases share mechanisms related to loss of tolerance, chronic B-cell activation, and production of autoantibodies. The presence of anti- Ro/SSA antibodies in the initial phase and persistent hypocomplementemia throughout the disease course highlight continuous immune activation. Interestingly, the absence of anti- dsDNA antibodies despite clinical lupus manifestations underscores the heterogeneity of autoantibody profiles in systemic lupus erythematosus and the importance of clinical judgment in diagnosis [5].

The development of systemic sclerosis in this patient was characterized by classical features including Raynaud's phenomenon, esophageal dysmotility, interstitial lung disease, and skin involvement. The transition from lupus to scleroderma phenotype has been described in overlap syndromes and may reflect a shift in immune pathways and fibrotic mechanisms [6]. The concomitant presence of celiac disease further supports the hypothesis of systemic immune dysregulation affecting multiple organ systems, including the gastrointestinal tract [7].

Therapeutically, the management of multiple autoimmune syndrome requires an individualized approach based on the predominant clinical manifestations. Immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil play a central role

in controlling systemic inflammation and preventing organ damage. Close monitoring is essential to balance efficacy and adverse effects, as illustrated by the hepatic toxicity observed during treatment.

This case highlights the importance of long-term follow-up in patients with autoimmune diseases, as new conditions may emerge over time. It also emphasizes the need for a multidisciplinary approach and a high index of suspicion for additional autoimmune diagnoses when new symptoms arise. Understanding the shared mechanisms among autoimmune diseases may provide insights into future therapeutic strategies targeting common pathways of immune dysregulation.

Declarations Funding

The author declares that no specific funding was received for the preparation of this manuscript.

Conflicts of Interest

The author declares no conflicts of interest related to this work. Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was not required for this case report according to institutional policies, as it describes a single patient without experimental intervention.

Consent to Participate

Written informed consent was obtained from the patient for clinical evaluation and use of anonymized data.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Use of Artificial Intelligence

The author used artificial intelligence (AI) tools to assist with language editing, grammar refinement, and organization of the manuscript. All content was critically reviewed, verified, and approved by the author, who takes full responsibility for the accuracy, integrity, and originality of the work.

Availability of Data and Materials

All relevant data are included within the manuscript. Additional information is available from the corresponding author upon reasonable request.

Author Contributions (CRediT taxonomy)

Jozélio Freire de Carvalho: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision.

Acknowledgements

The author thanks the patient for her cooperation and consent for publication of this case.

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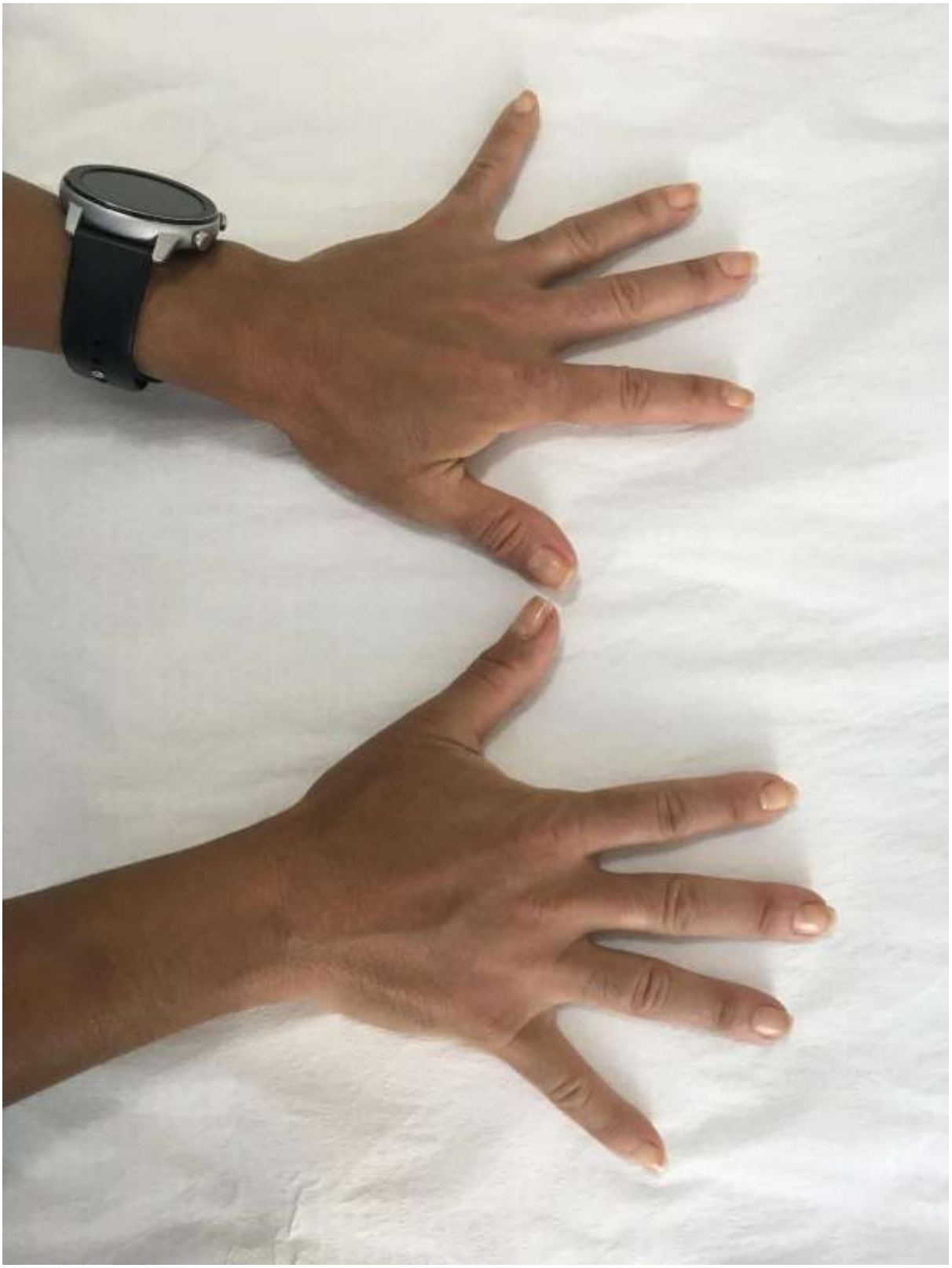

Figure 1 legend. Hand showing sclerodactyly with digital skin thickening and tapering of the fingers, consistent with systemic sclerosis.

Figure 2 legend. Facial involvement demonstrating microstomia and characteristic features of scleroderma, including reduced oral aperture and skin tightening.