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Cytokine-Based Regenerative Treatment in Primary Sjögren Syndrome: A Case Report of the Improvement of Anti-SSA Antibodies, Salivary Gland Swelling, and Hippocampal Atrophy

Takuji Shirasawa[1,2]*, Luis Carlos Aguilar Cobos[3]

[1]*Ochanomizu Health and Longevity Clinic, Tokyo 101-0062, Japan*

[2]*Shirasawa Anti-Aging Medical Institute, Tokyo 101-0062, Japan*

[3]*Livant Neurorecovery Center, Guadalajara, Mexico*

ABSTRACT

Background: Primary Sjögren syndrome is a systemic autoimmune disease that can involve the glandular, pulmonary, cardiovascular, autonomic, and central nervous systems.

Case presentation: A 75-year-old woman with primary Sjögren syndrome presented with fatigue, dry mouth, and dizziness and had salivary gland swelling, anti-SSA/Ro antibody positivity, pulmonary fibrosis, cardiovascular involvement, autonomic dysfunction, and marked hippocampal atrophy. The patient received cytokine-based treatment combined with low-dose prednisolone. Longitudinal assessments included serological, imaging, neurophysiological, autonomic, and clinical evaluations.

Results: During the six-year follow-up period, anti-SSA/Ro antibody status became negative, salivary gland swelling decreased, dry mouth and fatigue improved, serum cortisol levels recovered, neurophysiological hyperexcitability appeared reduced, and hippocampal and entorhinal morphology showed apparent longitudinal changes on imaging. Cardiovascular findings remained largely stable, with a subsequent decrease in BNP after administration of an additional cytokine-based formulation, whereas pulmonary imaging showed progression despite preserved pulmonary function. These findings describe temporal associations and do not establish treatment causality.

Conclusion: This single case suggests a possible temporal association between cytokine-based treatment combined with low-dose prednisolone and improvement in selected serological, glandular, autonomic, and neurological findings in primary Sjögren syndrome. Because causality cannot be inferred from one case, further controlled studies are needed to evaluate the safety, reproducibility, and potential clinical relevance of this approach.

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***Corresponding Author**

Takuji Shirasawa

Ochanomizu Health and Longevity Clinic, Tokyo 101-0062, Japan, and Shirasawa Anti-Aging Medical Institute, Tokyo 101-0062, Japan, E-mail: takujishirasawa@icloud.com

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INTRODUCTION

Sjögren syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands, resulting in dry mouth and dry eye [1,2]. Beyond sicca symptoms, the disease may involve multiple organs, including the lungs, nervous system, kidneys, joints, and cardiovascular system [2,3]. Fatigue, pain, autonomic dysfunction, and neuropsychiatric symptoms can substantially impair quality of life and are increasingly recognized as clinically important systemic manifestations of primary Sjögren syndrome [4,5]. Anti-SSA antibodies and salivary gland abnormalities are important diagnostic features, whereas systemic manifestations require careful longitudinal assessment [1]. Pulmonary involvement, including interstitial lung disease and airway disease, is among the major extraglandular complications and may occur independently of glandular disease activity [6]. Because Sjögren syndrome is clinically heterogeneous, comprehensive evaluation of glandular, immunological, neurological, pulmonary, and vascular findings is essential for accurate diagnosis, prognostic assessment, and individualized treatment planning [7].

Neurological involvement is an important extraglandular manifestation of primary Sjögren syndrome. Patients may present with peripheral neuropathy, autonomic dysfunction, cognitive complaints, mood-related symptoms, or central nervous system abnormalities. Brain MRI studies have reported white matter lesions, cortical atrophy, ventricular dilatation, and functional network alterations, although these findings are heterogeneous and not disease-specific [8]. In the present case, hippocampal atrophy and electrophysiological hyperexcitability may therefore reflect limbic involvement associated with systemic autoimmunity.

Anti-SSA/Ro antibodies are among the most important serological biomarkers in primary Sjögren syndrome. They reflect B-cell hyperactivity and are incorporated into the 2016 ACR/EULAR classification criteria, in which anti-SSA positivity carries a high diagnostic weight comparable to focal lymphocytic sialadenitis [9]. Anti-SSA antibodies are also associated with distinct clinical phenotypes, systemic activity, and extraglandular manifestations, although their predictive value may vary according to the detection assay used [10].

Pulmonary and vascular complications are clinically important extraglandular manifestations of primary Sjögren syndrome. Pulmonary involvement may include interstitial lung disease, airway disease, bronchiectasis, bronchiolitis, pulmonary hypertension, and lymphoproliferative disorders, and it can be associated with impaired quality of life and increased mortality [11]. Cardiovascular and vascular involvement may include subclinical myocardial dysfunction, vascular injury, pulmonary hypertension, and increased cardiovascular risk, requiring careful cardiopulmonary monitoring [12]. Therefore, high-resolution CT, pulmonary function testing, echocardiography, and vascular imaging are useful for longitudinal risk assessment in patients with systemic Sjögren syndrome.

Current treatment for Sjögren syndrome remains centered on symptomatic management of sicca symptoms, fatigue, pain, and organ-specific systemic disease, with topical ocular therapy, saliva substitutes, secretagogues, hydroxychloroquine, glucocorticoids, and immunosuppressants selected according to disease severity [13]. Recent therapeutic development has increasingly focused on targeted immune modulation. Ianalumab, a BAFF-receptor–targeting B-cell-depleting antibody, has shown encouraging results in clinical trials, and dazodalibep, a CD40 ligand antagonist, has been reported to improve systemic activity and symptom burden in a phase 2 trial [14]. Emerging strategies also include inhibition of B-cell survival pathways, interferon signaling, co-stimulatory pathways, kinase signaling, IgG recycling, and regenerative approaches, suggesting a gradual transition from symptomatic care toward more mechanism-based and individualized therapy [15]. In the present case, cytokine-based treatment combined with low-dose prednisolone was followed by changes in anti-SSA antibody status, salivary gland swelling, hippocampal morphology, and symptoms such as dry mouth and fatigue. Because this is a single case observation, these findings should be interpreted as hypothesis-generating rather than evidence of therapeutic efficacy.

METHOD

The cytokine and exosome cocktail used in this case study was designed and developed by Luis Carlos Aguilar Cobos at the Livant Neurorecovery Center, Mexico, as previously described [16-19]. Six cytokine- and exosome-based formulations were administered. The formulations included components selected for potential relevance to GABAergic and glutamatergic neurogenesis, and OST and Muss formulations contained progranulin, a factor implicated in neurogenic processes in the frontal and temporal cortices.

The cocktail comprised exosomal components derived from young adult porcine tissues and included microRNAs such as miR-124, miR-126, miR-146a, miR-29, let-7, and miR-34a. Treatment was administered sublingually three times daily.

CASE DESCRIPTION

Initial assessment

A 75-year-old woman presented to the Ochanomizu Health and Longevity Clinic on August 22, 2019, with memory complaints, fatigue, dry mouth, and dizziness. Her medical history included Hashimoto thyroiditis–associated hypothyroidism in her 20s, primary Sjögren syndrome in her 30s, lichen planus at 62 years of age, dyslipidemia at 65 years of age, and vitreoretinal and cataract surgery at 73 years of age.

Neurological examination on August 22, 2019, showed no objective memory impairment. The Mini-Mental State Examination score was 30/30, and the Cognitrax total score was 97.3. Domain scores for verbal memory, reasoning, executive function, cognitive flexibility, reaction time, motor speed, attention, and working memory were not impaired (Figure 1B).

Baseline laboratory evaluation included a complete blood count and blood chemistry testing, which showed preserved hepatic, renal, and hematopoietic function and no evidence of nutritional deficiency. The serum B-type natriuretic peptide (BNP) level was 34.9 pg/mL. Thyroid function was within the reference range, with thyroid-stimulating hormone 3.77 μIU/mL, free triiodothyronine 2.70 pg/mL, and free thyroxine 1.19 ng/dL. Serum cortisol was low at 4.27 μg/dL, with adrenocorticotropic hormone 12.8 pg/mL (Figure 1A). Preliminary genetic analysis showed an APOE ε3/ε3 genotype. Immunological testing showed elevated anti-thyroglobulin antibody levels of 127 IU/mL, anti-thyroid peroxidase antibody levels of 112 IU/mL, anti-SSA/Ro antibody levels of 19.7 U/mL, and an antinuclear antibody titer of 1:1280 with a centromere pattern, supporting the diagnoses of primary Sjögren syndrome and Hashimoto thyroiditis.

CT performed on August 24, 2019, showed salivary gland swelling (Figure 6B). Together with dry mouth and serological findings, this supported the diagnosis of primary Sjögren syndrome.

Chest CT on August 24, 2019, showed mild-to-moderate subpleural fibrosis in the posterior segment of the left lower lobe and mild fibrosis in segment 6 of the right lung (Figure 7A), consistent with primary Sjögren syndrome–associated interstitial lung disease.

A CT scan of the thoracic spine performed on August 24, 2019, revealed scoliosis at the Th3-4 and Th4-5 levels (Figure 7E). Given the absence of a documented history of trauma and the presence of age-related degenerative changes, these findings were considered unlikely to be attributable to traumatic injury.

A CT scan of the heart and aorta performed on August 24, 2019, revealed dilatation of the ascending aorta. The ascending aorta showed moderate dilatation at the level of the coronary arteries, with a vertical diameter of 34.4 mm and a horizontal diameter of 35.6 mm (Figure 8B, C). By comparison, the descending aorta measured 26.7 mm vertically and 25.1 mm horizontally (Figure 8B, C).

Cytokine-based treatment and follow-up

The patient was diagnosed with primary Sjögren syndrome with concomitant Hashimoto thyroiditis. As shown in Figure 1C, cytokine-based formulations were administered sublingually three times daily. Gabatrof (ADPK) 2.0 mL and Epatrof (H23 AZ) 1.0 mL were administered three times daily from August 22, 2019, to April 14, 2022. Gabatrof (EPI) 1.0 mL was administered three times daily from December 18, 2019, to April 14, 2022. OST 1.0 mL was administered three times daily from June 18, 2019, to April 14, 2022. Levothyroxine sodium 25 μg/day was prescribed for hypothyroidism.

During cytokine-based treatment, fatigue and orthostatic symptoms improved, and serum cortisol levels recovered (Figure 1A). Cognitive performance remained stable, including verbal memory, reasoning, executive function, cognitive flexibility, reaction time, motor speed, attention, and working memory (Figure 1B). Mini-Mental State Examination scores remained 30/30 throughout the treatment period.

Neurophysiological assessment on September 30, 2022, showed increased P300 responses over frontopolar, frontal, and parietal electrodes after cytokine-based treatment compared with pretreatment recordings (Figure 2A, B). Pretreatment hyperexcitable responses during attention and emotional processing tasks were attenuated after treatment across attention-related and emotional stimuli, including joy, sadness, anger, anxiety, and neutral expression (Figure 2C, D).

Hippocampal morphological assessment on September 25, 2021, showed apparent changes in the right hippocampal head and neck and the medial tip of the left hippocampus

compared with baseline imaging (Figure 3C, D). MRI-based virtual endoscopic views obtained on May 13, 2025, showed further apparent changes in bilateral hippocampal and entorhinal morphology (Figure 3E, F). Baseline hippocampal atrophy was not accompanied by measurable memory impairment, and these imaging findings should be interpreted as exploratory longitudinal observations rather than evidence of structural regeneration or treatment causality.

Dry mouth and dry eye improved during cytokine-based treatment with Renagen Spleen and prednisolone. Anti-SSA/Ro antibody levels normalized on July 7, 2025 (Figure 5A). Follow-up CT on September 7, 2025, showed reduced salivary gland swelling compared with the August 24, 2019, CT findings (Figure 6B).

Chest CT on July 7, 2025, showed imaging findings interpreted as progression of primary Sjögren syndrome–associated interstitial lung disease, with subpleural lesions in the left S2, left S6, and right S6 segments. Bronchial assessment showed slight dilatation of the left lower bronchial branches (Figure 7C), and CT-based virtual bronchoscopy showed airway sputum (Figure 7D). Pulmonary function testing on July 7, 2025, showed preserved pulmonary function, with percent predicted vital capacity of 88.4%, percent predicted forced expiratory volume in 1 second of 80.92%, and a normal flow-volume curve (Figure 7C, D).

Follow-up CT of the thoracic spine showed no clear pathological progression after the initial evaluation on August 24, 2019. Thoracic scoliosis at the T3–T5 levels appeared less pronounced on follow-up imaging after orthopedic realignment (Figure 7E, F).

Because primary Sjögren syndrome may involve the cardiovascular system, BNP levels and cardiovascular imaging were monitored. Baseline CT of the heart, aorta, and pulmonary artery on August 24, 2019, showed ascending aortic dilatation (Figure 8B, C). During cytokine-based treatment, BNP increased to 87.9 pg/mL on July 7, 2025. Follow-up 3D CT on the same date showed no clear imaging evidence of progression in the assessed cardiovascular structures (Figure 8D, E). CORAGEN, an additional cytokine-based formulation, was then administered as shown in Figure 9. BNP decreased to 48.3 pg/mL on March 9, 2026; this temporal change should be interpreted cautiously and does not establish a treatment effect.

DISCUSSION

In this case study, a 75-year-old woman presented to our clinic with fatigue and dry mouth and underwent comprehensive clinical evaluation, including MRI, CT, EEG, blood testing, immunological assessment, and neurological examination. The findings were compatible with primary Sjögren syndrome involving glandular, pulmonary, cardiovascular, neurological, immunological, and skeletal manifestations. The patient received cytokine-based treatment in combination with low-dose prednisolone. During follow-up, anti-SSA/Ro antibody status became negative, salivary gland swelling resolved, hippocampal and entorhinal morphology appeared improved on imaging, and symptoms such as dry mouth and fatigue improved. These observations represent a temporal association and should not be interpreted as evidence of causality. Because this was a single uncontrolled case involving concomitant treatment, spontaneous fluctuation, background clinical care, measurement variability, and the effects of low-dose prednisolone may have contributed to the observed changes. To our knowledge, longitudinal assessment combining serological, glandular, neurological, and imaging findings following this treatment approach has not been extensively described. Because anti-SSA/Ro antibodies are important serological biomarkers in primary Sjögren syndrome [1], these observations may be hypothesis-generating but require confirmation in larger controlled studies.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that has been implicated in immune tolerance through effects on antigen-presenting cells, effector T cells, and B cells [20]. In Sjögren syndrome, the role of IL-10 is likely context dependent because regulatory mechanisms that restrain tissue-damaging inflammation may coexist with B-cell hyperactivity and autoantibody production. Regulatory T cells (Tregs), particularly FOXP3-positive CD4+ T cells, are an important cellular source and target of IL-10 and contribute to peripheral tolerance by suppressing autoreactive T cells and limiting B-cell activation [21]. In the present case, loss of anti-SSA/Ro antibody positivity, improvement in dry mouth, and resolution of salivary gland swelling after cytokine-based treatment combined with low-dose prednisolone may be compatible with improved immune regulation in the glandular compartment. However, this interpretation is speculative because circulating Treg numbers, Treg suppressive function, IL-10 concentration, B-cell subset activity, and salivary gland immune-cell infiltration were not directly measured. Therefore, the IL-10–Treg axis should be regarded only as a possible explanatory framework rather than a demonstrated mechanism in this patient. Moreover, progression of Sjögren syndrome–associated interstitial

lung disease despite improvement in anti-SSA/Ro antibody status and salivary gland morphology suggests that glandular, serological, and pulmonary disease activity may follow partly dissociated trajectories. Future studies should include longitudinal assessment of IL-10, Treg phenotype and function, B-cell activation markers, and organ-specific outcomes before mechanistic conclusions can be drawn.

Fatigue in Sjögren syndrome is a clinically important symptom that may be influenced by multiple factors, including systemic inflammation, neuroimmune dysregulation, central nervous system involvement, sleep disturbance, mood-related symptoms, autonomic dysfunction, and comorbid conditions [2,4]. Previous reviews have emphasized that fatigue is one of the most disabling symptoms in Sjögren syndrome and is frequently associated with depression, sleep disturbance, reduced activity levels, and impaired quality of life [4]. Central nervous system involvement is also recognized as an extraglandular manifestation of primary Sjögren syndrome; MRI studies have reported white matter hyperintensities, cortical atrophy, ventricular dilatation, and microstructural alterations detected by diffusion tensor imaging and resting-state functional MRI, although the neuroimaging pattern is heterogeneous and not disease-specific [8]. Thus, the fatigue observed in this patient may have had multifactorial contributors, and the available data do not allow attribution to a single mechanism.

Cognitive and affective symptoms in Sjögren syndrome have been linked to depression, anxiety, sleep disturbance, and hippocampal-type cognitive profiles, suggesting that limbic network dysfunction may contribute to neuropsychiatric symptoms in some patients [22]. In the present case, hippocampal atrophy was observed on MRI, and electrophysiological testing showed hyperexcitability during emotional and attention tasks (Figure 2). These findings raise the possibility that hippocampal or limbic system abnormalities (Figure 3) were related to the patient's fatigue, altered emotional responsiveness, or attentional dysregulation (Figure 2). However, this relationship remains uncertain. Alternative explanations include age-related neuroanatomical changes, comorbid disease, medication effects, stress-related physiology, technical differences in image acquisition or analysis, and test–retest variability.

Sjögren syndrome has been reported to be associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and altered cortisol responses, which may contribute to stress vulnerability in some patients [23]. During acute stress, cortisol is secreted from the adrenal glands through activation of the HPA axis. Under chronic stress, HPA-axis feedback may become impaired and cortisol signaling may become dysregulated [24]. Experimental and clinical studies have also implicated glucocorticoid receptor–mediated signaling in stress-related hippocampal dysfunction [24]. In the present case, hyperexcitability observed during attention and emotion-processing tasks could be compatible with altered limbic network regulation, but the underlying cellular or endocrine mechanism cannot be established from these data. After treatment, hippocampal and entorhinal morphology appeared improved, and attention-related and emotional electrophysiological responses appeared less hyperexcitable (Figure 2C, 2D). Because short-term memory impairment was not evident at baseline (Figure 1), these findings may suggest that limbic network abnormalities, if present, were more closely related to attention, emotional regulation, motivation, initiative, or fatigue-related symptoms than to overt memory impairment. This interpretation remains exploratory and should be tested in future studies with standardized neuropsychological, imaging, endocrine, and electrophysiological assessments [25].

In Sjögren syndrome, activated B cells may form lymphoid follicles within the salivary glands, contributing to local autoimmune inflammation and autoantibody production [25]. Activated B lymphocytes are associated with anti-SSA/Ro antibody production (Figure 6D), and anti-SSA/Ro antibodies have also been discussed in relation to selected central nervous system manifestations through mechanisms such as microglial activation and axonal injury [26]. In the present case, cytokine-based therapy combined with low-dose prednisolone was followed by seronegativity for anti-SSA/Ro antibodies (Figure 6). Concurrent changes in attention-related responses (Figure 2C), emotional hyperexcitability (Figure 2D), autonomic regulation (Figure 5), and serum cortisol levels (Figure 1) may reflect broader clinical fluctuation or systemic changes during follow-up. However, these observations do not establish suppression of B-cell activity, reversal of autoimmune pathology, or a direct treatment effect. Mechanistic studies would be required to clarify whether immune modulation contributed to the observed clinical and imaging changes.

Pulmonary fibrosis can occur as a complication of Sjögren syndrome, and interstitial lung disease is recognized as one of the major extraglandular pulmonary manifestations of primary Sjögren syndrome [3]. In the present case, subpleural interstitial lung disease was observed in the left lower lobe and right S6 segment at the initial assessment

(Figure 7A). Repeat chest CT performed on July 7, 2025, showed that the interstitial lung disease appeared to have progressed. This progression contrasted with improvement in salivary gland swelling and anti-SSA/Ro antibody status, suggesting that pulmonary disease activity may not parallel glandular or serological changes in all patients. Although the patient had cough and sputum on July 7, 2025, sputum was also observed within the airway on CT-based virtual bronchoscopy images, and mild dilatation of the left lower bronchial branches was noted. These findings are compatible with reports that Sjögren syndrome may involve both lung parenchyma and the airways, including tracheobronchial disease, bronchiectasis, bronchiolitis, and obstructive airway disease [3]. In this case, chronic obstructive airway changes may have coexisted with interstitial lung disease (Figure 7C, 7D), although this cannot be confirmed without additional longitudinal pulmonary testing and specialist evaluation. On the same day, thoracic spine CT showed less apparent scoliosis compared with the initial assessment (Figure 7F). Because no pathological progression of osteoporosis was observed, this change may have reflected postural, muscular, positioning-related, or measurement-related factors rather than a direct treatment effect.

Among the extraglandular complications of Sjögren syndrome, cardiovascular involvement is clinically important and may contribute to morbidity and mortality. In the present case, the initial assessment showed mildly elevated serum B-type natriuretic peptide (BNP) levels (Figure 8A). CT performed at the initial evaluation demonstrated moderate dilatation of the ascending aorta (Figure 8B, 8C). Morphological assessment suggested that the lesion was not typical of either a dissecting aortic aneurysm or an atherosclerotic lesion; it was interpreted as a degenerative arterial change that may have been related to Sjögren syndrome or to non–Sjögren-related vascular aging. After the serum BNP level increased to 87.9 pg/mL on July 7, 2025, follow-up CT was performed. Comparison with baseline CT findings showed no apparent pathological progression in the ascending aorta, left ventricle, pulmonary artery, or descending aorta (Figure 8D, 8E). Echocardiography performed on August 12, 2025, demonstrated a left ventricular ejection fraction of 66.9%, indicating preserved left ventricular systolic function. Moderate dilatation of the ascending aorta, together with mild aortic regurgitation, may have contributed to cardiac workload, although the clinical significance of this finding remains uncertain. In this case, CORAGEN, a cytokine-based formulation, was administered after the cardiovascular findings were reviewed. The components of CORAGEN are summarized in Figure 9. CORAGEN contains cytokines and growth factors, including SDF-1, HGF, IGF-1, IGF-2, FGF-2, IL-10, and PGRN, which have been implicated in angiogenesis, vascular repair, endothelial function, and modulation of vascular inflammation in prior studies [27-32]. CORAGEN also contains microRNAs, including miR-126, miR-146a, miR-29, let-7, and miR-34a, which have been associated with vascular integrity, angiogenic signaling, inflammatory regulation, extracellular matrix remodeling, endothelial responses, and vascular aging [33-37]. On this basis, CORAGEN could be hypothesized to influence vascular biology, including endothelial glycocalyx-related pathways, but this was not directly assessed in the present patient. Although BNP levels subsequently decreased, this temporal relationship should be interpreted cautiously. Spontaneous fluctuation, background management, hydration status, cardiac loading conditions, assay variability, and other clinical factors may have contributed to the observed BNP change.

This case is notable for the longitudinal observation of changes across multiple domains of primary Sjögren syndrome, including glandular symptoms, anti-SSA/Ro antibody status, central nervous system findings, autonomic regulation, and salivary gland morphology. These findings suggest that comprehensive assessment of Sjögren syndrome may be useful beyond sicca symptoms and routine serological testing, particularly when patients present with fatigue, emotional dysregulation, dizziness, or cognitive complaints. However, the observations should be interpreted with caution. This report involved a single patient, lacked a control group, included concomitant low-dose prednisolone, and relied on several imaging and physiological measures that may be influenced by technical and biological variability. Therefore, anti-SSA/Ro antibody levels, neurophysiological findings, autonomic measures, and imaging-based markers should be considered exploratory longitudinal indicators rather than validated markers of treatment response in this setting. Larger prospective studies with standardized outcome measures are required to determine whether cytokine-based regenerative treatment has reproducible safety, biological activity, or clinical efficacy in primary Sjögren syndrome.

Future studies should evaluate cytokine-based regenerative treatment in larger prospective cohorts with appropriate control groups and standardized clinical, serological, imaging,

neurophysiological, autonomic, and pulmonary outcome measures. Particular attention should be given to mechanistic profiling of the IL-10–Treg–B-cell axis, including longitudinal assessment of circulating and tissue-resident Tregs, IL-10 signaling, B-cell activation markers, BAFF-related pathways, and anti-SSA/Ro antibody titers. Because pulmonary lesions progressed despite improvement in salivary gland swelling and anti-SSA/Ro antibody status in the present case, future research should examine organ-specific treatment responses and determine whether glandular, serological, neurological, cardiovascular, and pulmonary manifestations follow different disease trajectories. Controlled studies that separate the effects of cytokine-based treatment from low-dose prednisolone and other background clinical factors are needed to clarify safety, biological activity, mechanisms of action, and durability of clinical response in primary Sjögren syndrome.

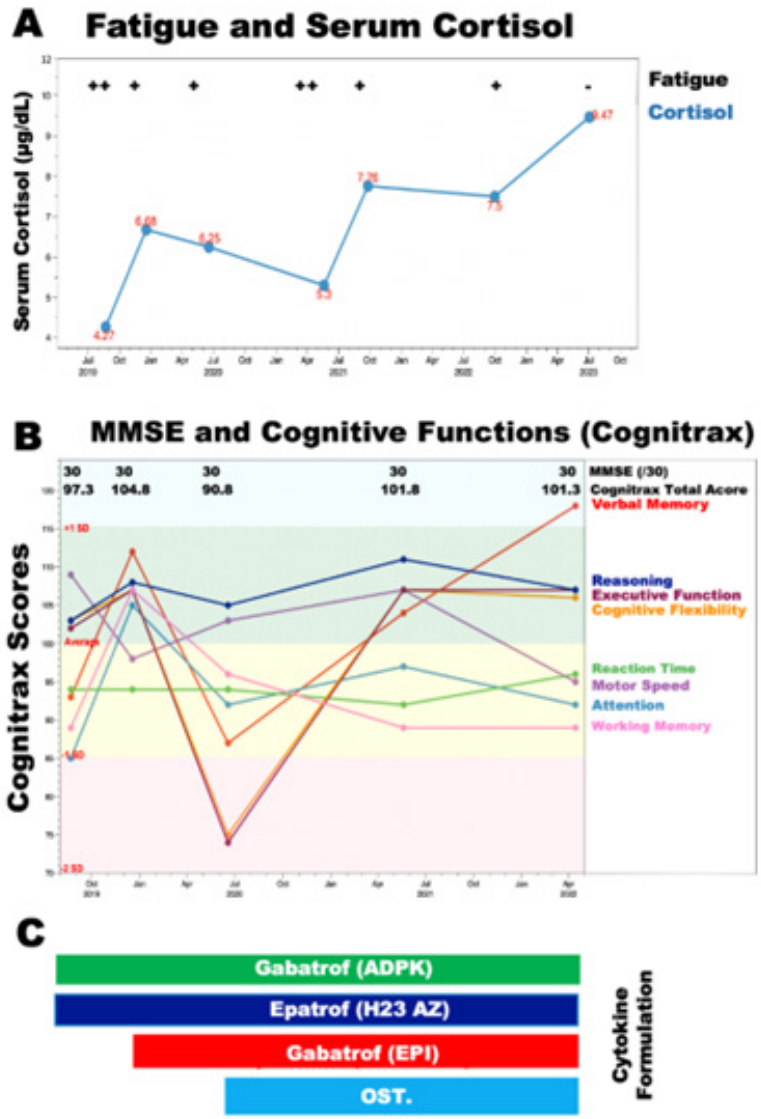

Figure 1

A: The serum cortisol values are displayed graphically during cytokine-based therapy. The fatigue symptom and body weight are annotated in the upper part of the graph.

B: The present study will examine the effects of cytokine-based therapy on cognitive function, as measured by the Mini-Mental State Examination (MMSE) score, in patients before and after treatment. The cognitive function of the participants was evaluated on August 22, 2019; December 18, 2019; June 18, 2020; May 20, 2021; and April 14, 2020, using the Cognitrax

and the Mini-Mental State Examination (MMSE). The scores from the Mini-Mental State Examination (MMSE) are annotated in the upper section of the graph. The cognitive flexibility (yellow), executive function (brown), reasoning (dark blue), attention (light blue), verbal memory (red), motor speed (plum), reaction time (green), and working memory (magenta) scores of Cognitrax are chronologically illustrated as line graphs with different colors. The mean Cognitrax score among the Japanese population is 100. The population under consideration is of the same age. The color green signifies the zone that encompasses the mean ± 1 standard deviation. Yellow denotes the zone ranging from 1 standard deviation to 2 standard deviations below the mean, while blue indicates the zone that extends +1 standard deviation above the mean.

C: The various cytokine formulations that were administered are illustrated below.

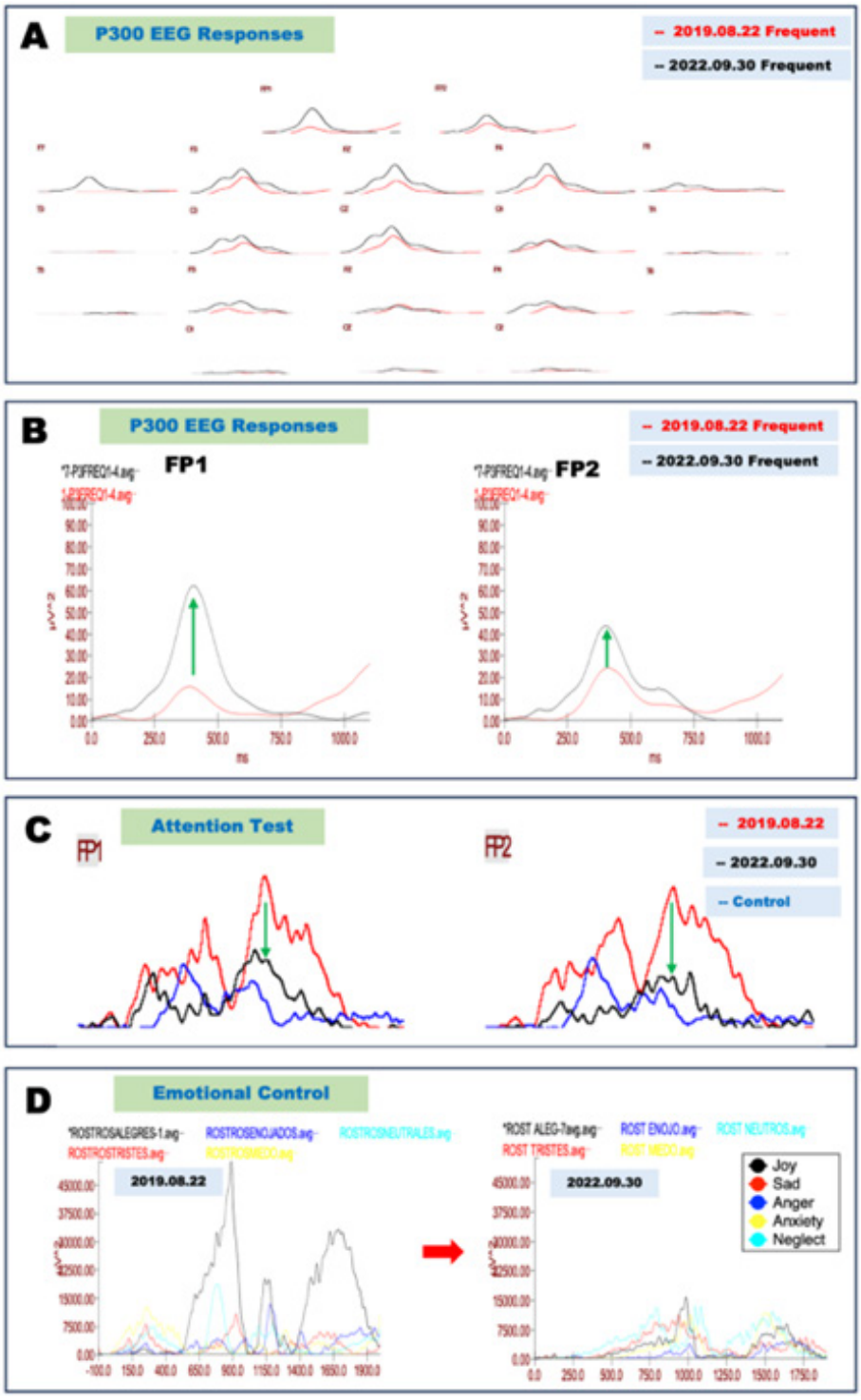

Figure 2: Neurophysiological evaluations before and after cytokine-based treatment

A: Electrophysiological evaluation of P300 electroencephalogram (EEG) responses during cytokine-based treatment. Prior to treatment, on August 22, 2019, the P300 EEG responses to a frequent stimulus (low-pitched sound) are depicted as red lines. Following treatment, on September 30, 2022, the EEG responses are illustrated as black lines.

B: A magnified view of the recordings from the frontopolar electrodes is shown. The P300 responses recorded on September 30, 2022 (black lines) appeared increased compared with those recorded on August 22, 2019 (red lines; left, left frontopolar leads; right, right frontopolar leads).

C: Attention test recordings before and after cytokine-based treatment. Hyperexcitable responses recorded on August 22, 2019, in the frontopolar electrodes (FP1 and FP2) appeared attenuated on September 30, 2022, compared with control responses.

D: Emotional processing analysis during follow-up. Electroencephalograms were recorded at the left frontopolar electrode while the patient viewed facial expressions, including happy, sad, angry, neutral, and worried expressions. Recordings are shown for August 22, 2019 (left panel) and September 30, 2022 (right panel).

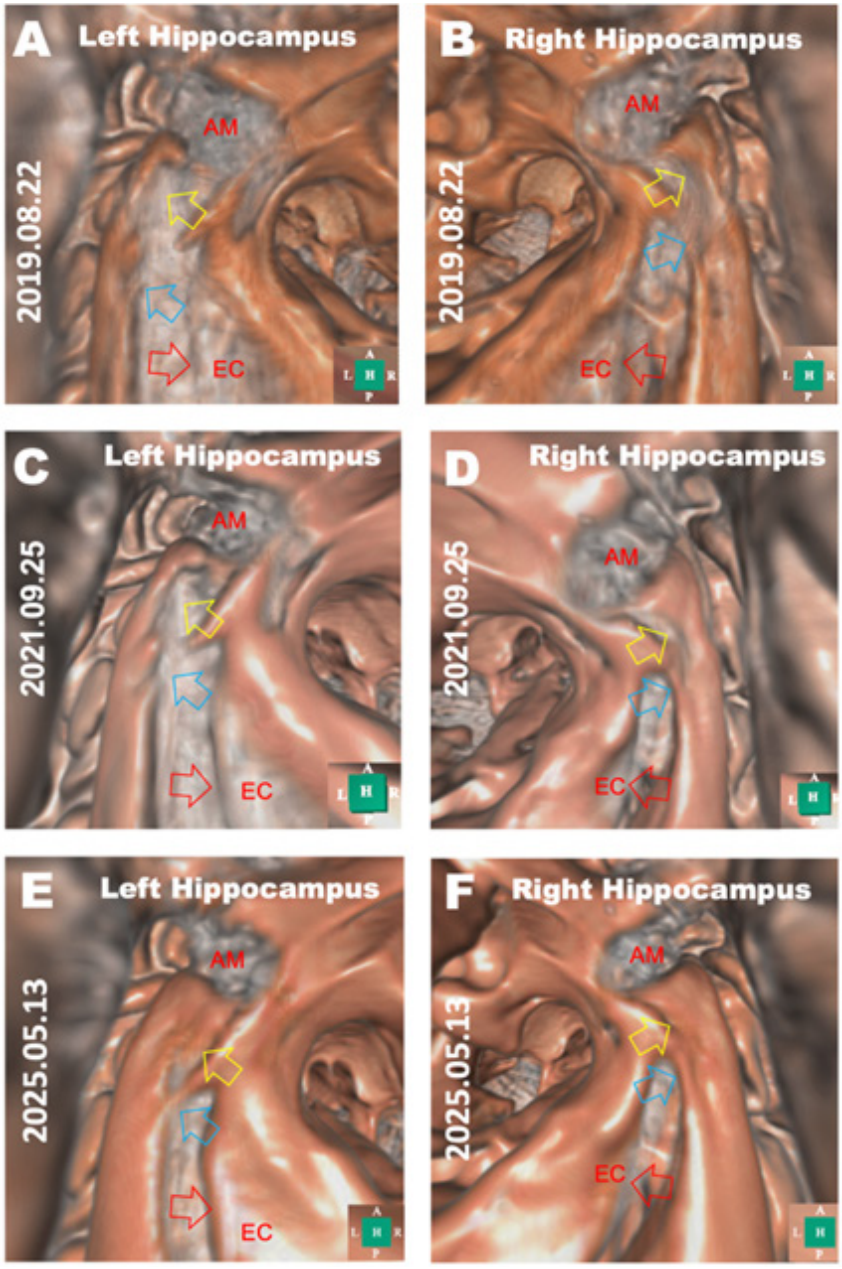

Figure 3: Morphological evaluation of the hippocampus during longitudinal follow-up

A., B: The endoscopic in silico images of the left hippocampus (A) and right hippocampus (B) reveal atrophy at the head (yellow arrow), neck portion (blue arrow), and entorhinal cortex (red arrow) on August 22, 2019.

C, D: Endoscopic in silico images of the left hippocampus (C) and right hippocampus (D) obtained on September 25, 2021. Compared with baseline imaging, apparent morphological changes were observed in the head (yellow arrow), neck portion (blue arrow), and entorhinal cortex (red arrow).

E, F: Endoscopic in silico images of the left hippocampus (E) and right hippocampus (F) obtained on May 13, 2025. Further apparent morphological changes were observed in the head (yellow arrow), neck portion (blue arrow), and entorhinal cortex (red arrow). These imaging observations do not establish structural regeneration or treatment causality.

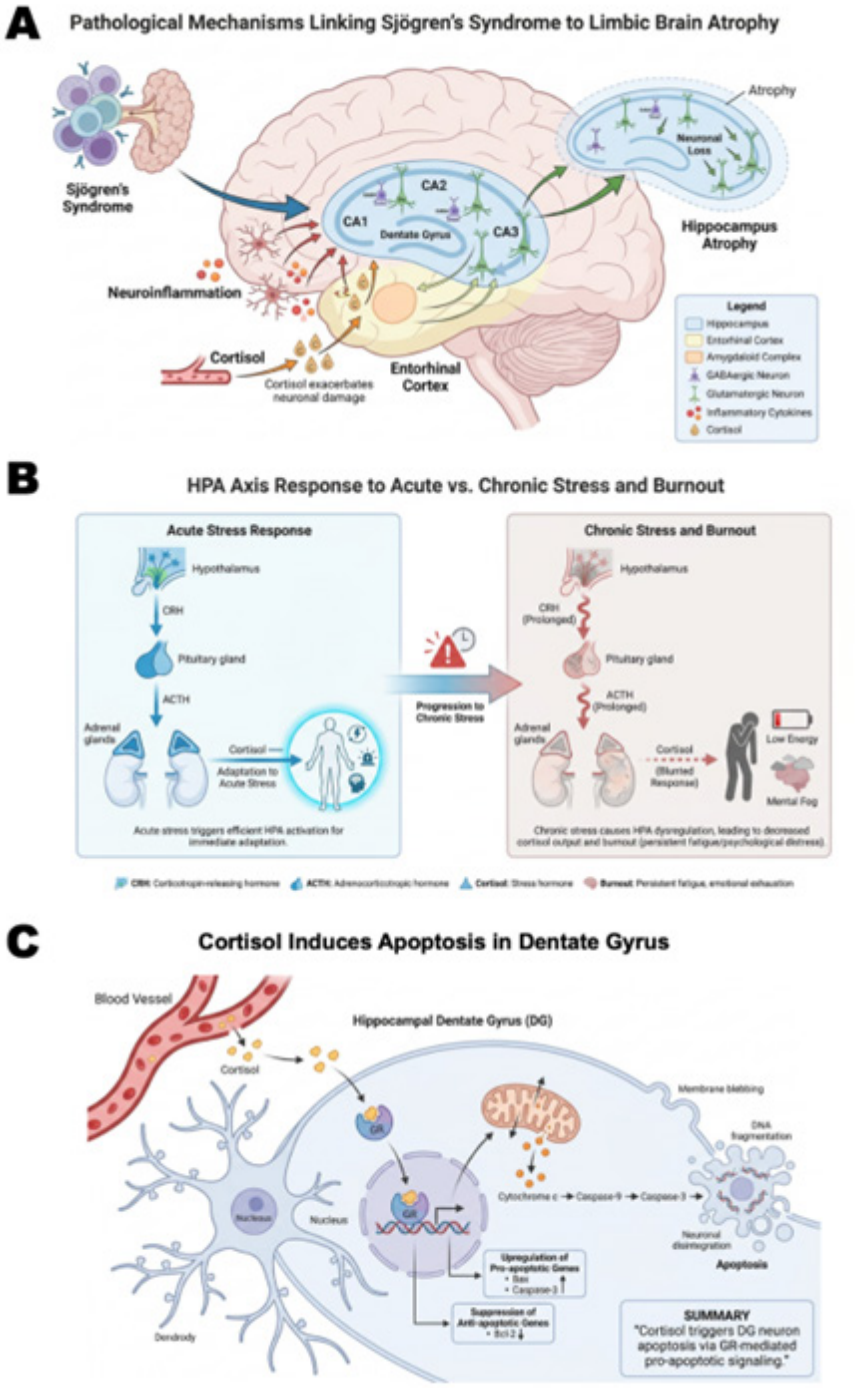

Figure 4: Possible mechanisms linking primary Sjögren syndrome to limbic brain atrophy. The figure was created using Figurelabs.ai.

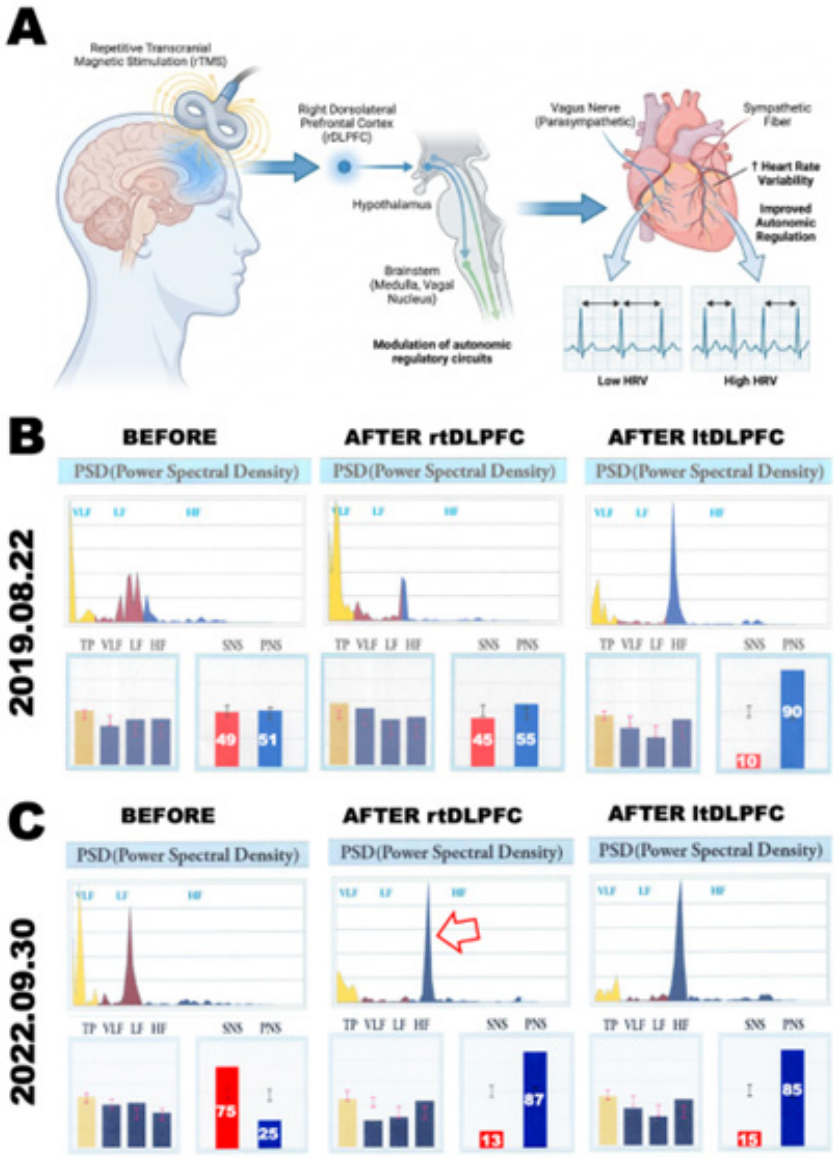

Figure 5:

A: The present study investigates the impact of repetitive transcranial magnetic stimulation (rTMS) applied to the right or left dorsolateral prefrontal cortex on autonomic regulation and heart rate variability. The figure was created using Figurelabs.ai.

B: Autonomic regulation was assessed via a test before and after repetitive transcranial magnetic stimulation (rTMS) to the right and left dorsolateral prefrontal cortex (DLPFC) on August 22, 2019.

C: Autonomic regulation was assessed via a test before and after repetitive transcranial magnetic stimulation (rTMS) to the right and left dorsolateral prefrontal cortex (DLPFC) on September 30, 2022.

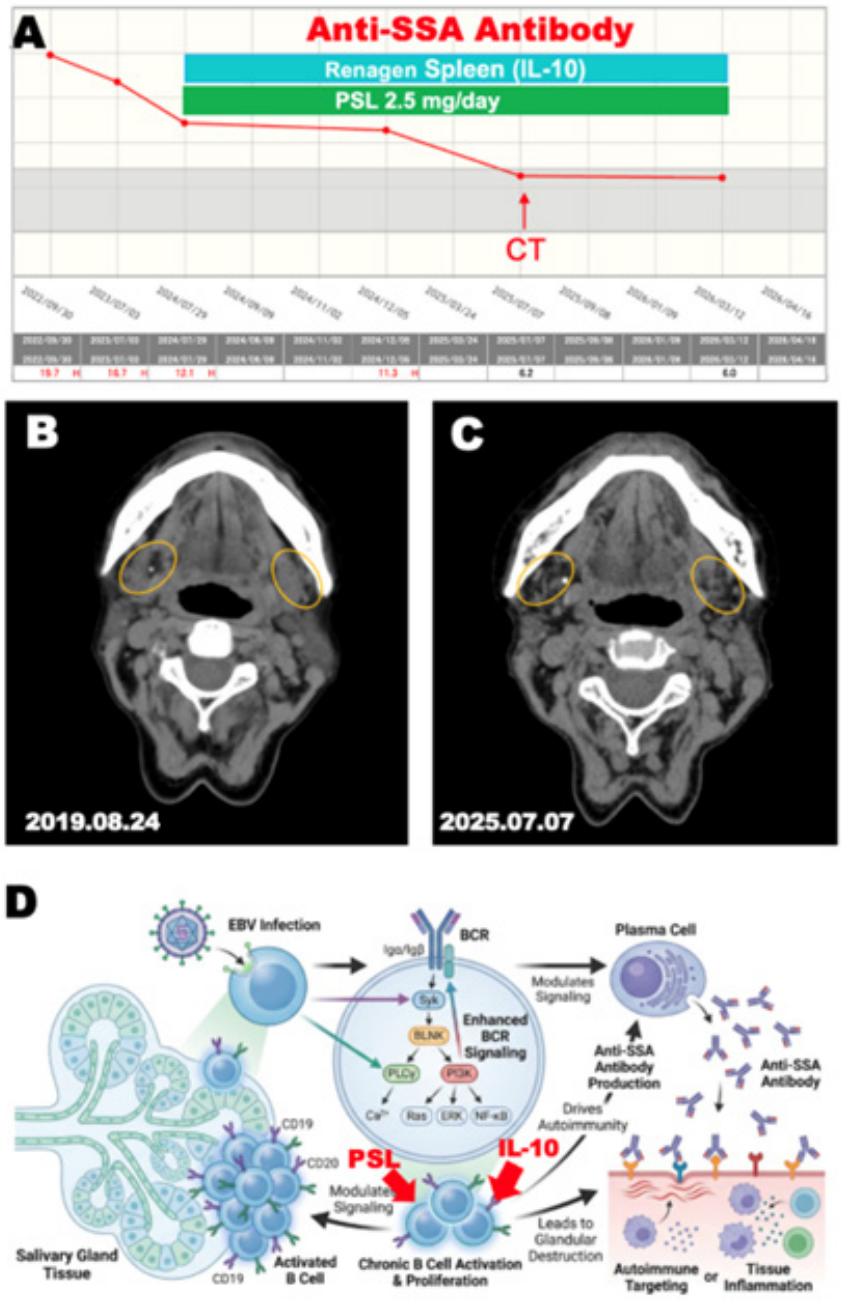

Figure 6:

A: The serum anti-SSA antibody titers are presented in graphical form during cytokine-based therapy.

B, C: CT images of the salivary glands obtained on August 24, 2019, and July 7, 2025, during longitudinal follow-up.

D: The etiology of Sjögren syndrome is multifactorial, involving a complex interplay between environmental and genetic factors, as well as viral infections. Research has identified a role for Epstein-Barr virus (EBV) infection, B-cell receptor (BCR) signaling, and chronic salivary gland B-cell infiltration in the pathogenesis of this condition. The figure was created using Figurelabs.ai.

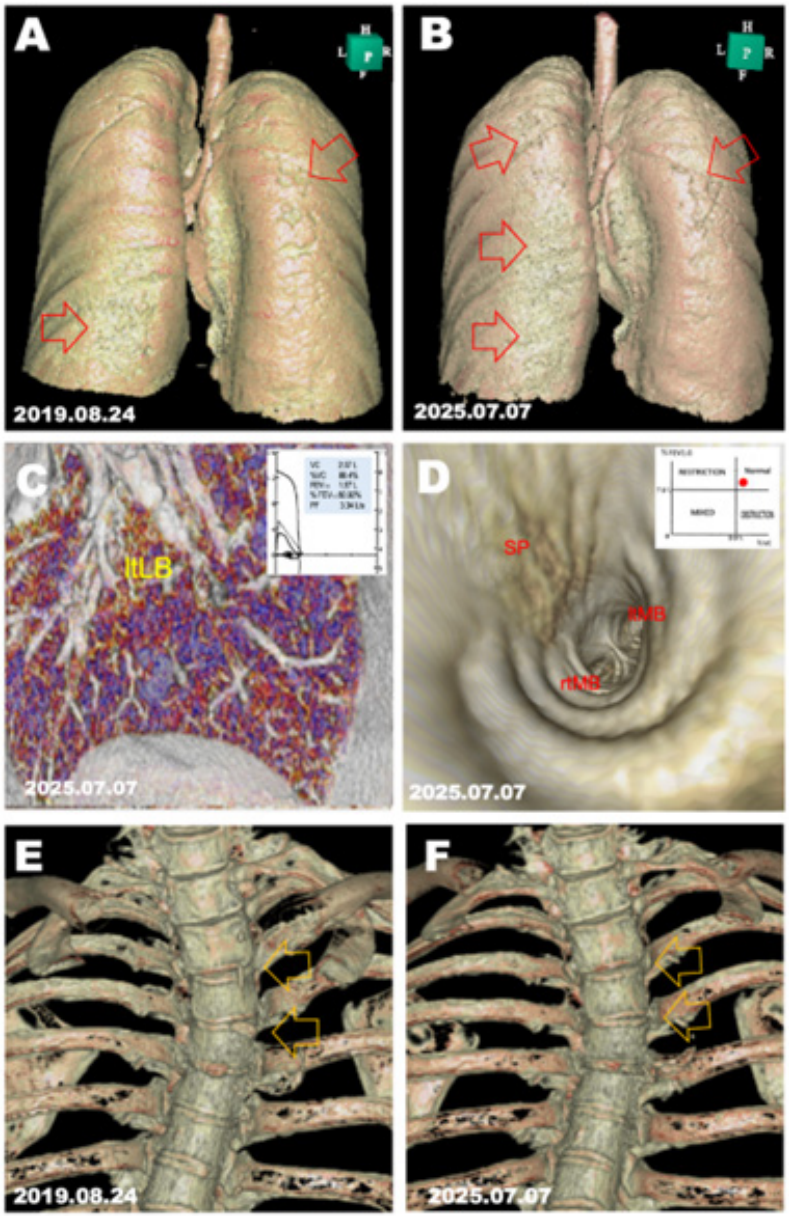

Figure 7:

A, B: CT scans obtained on August 24, 2019 (left panel) and July 7, 2025 (right panel). Three-dimensional lung structures in posterior view were reconstructed in silico using Expert INTAGER software from 1-mm CT slices. Fibrotic lesions on the posterior pleural surface are indicated by red arrows.

C: A frontal cutting view of the bronchus and lung was reconstructed from a series of CT slices recorded on July 7, 2025. The right lower bronchus exhibited mild dilation. The peak flow curve is illustrated in the right upper islet.

D: The following image depicts a bronchoscopy view of the main trachea, accompanied by views of the carina, the right main bronchus, and the left main bronchus. The summary of pulmonary function test is illustrated in the right upper islet.

E, F: CT scans of the thoracic vertebrae obtained on August 24, 2019 (left panel) and July 7, 2025 (right panel). Scoliosis between Th3–4 and Th4–5 appeared less pronounced on follow-up imaging; this observation does not establish a treatment effect.

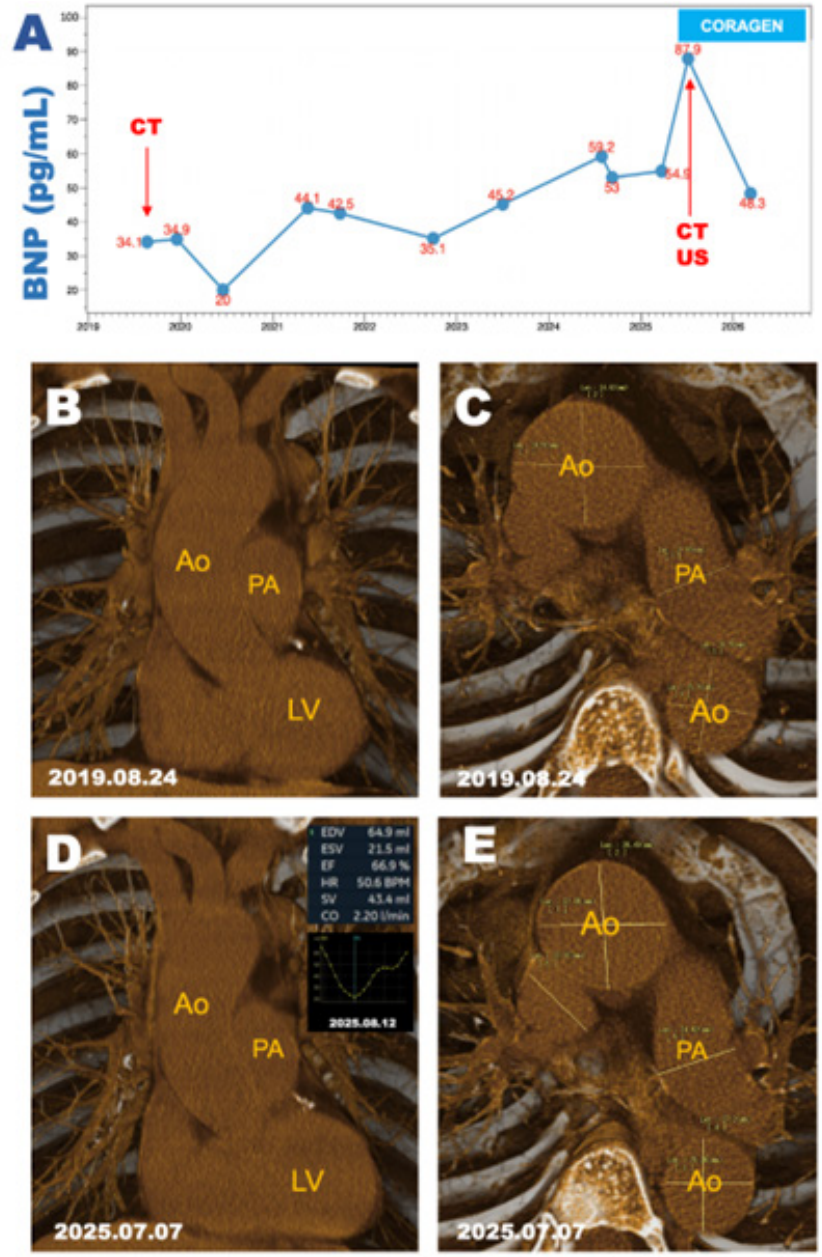

Figure 8

A: Serum BNP levels are presented graphically during follow-up. Administration of CORAGEN is indicated in the upper right corner.

B, C, D, E: The following are 3D-CT frontal and axial images of the heart and aorta, with the initial scan taken on August 24, 2019, and the subsequent CT scan taken on July 7, 2025. Cardiac US data is presented in right upper islet of Figure 8D.

Figure 9: Components of CORAGEN and proposed mechanisms potentially relevant to vascular pathology. The figure was created using Figurelabs.ai.

CONCLUSION

In this case study, a 75-year-old woman presented with fatigue and dry mouth and was found to have clinical features consistent with primary Sjögren syndrome involving glandular, pulmonary, cardiovascular, neurological, immunological, and skeletal findings. The patient received cytokine-based treatment in combination with low-dose prednisolone. During follow-up, anti-SSA/Ro antibody status became negative, salivary gland swelling decreased, hippocampal and entorhinal morphology showed apparent

longitudinal changes on imaging, and symptoms such as dry mouth and fatigue improved. These observations suggest a possible temporal association between the treatment regimen and changes in selected systemic findings. However, because this report describes a single uncontrolled case with concomitant therapies, causality cannot be inferred. Further prospective studies with standardized outcome measures are required to evaluate the safety, reproducibility, and potential clinical relevance of this approach.

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ETHICAL APPROVAL OF STUDIES AND INFORMED CONSENT

Written informed consent was obtained from the patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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