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OVERLAP-СИНДРОМ — РЕДКОЕ СОЧЕТАНИЕ ТРЕХ АУТОИММУННЫХ ПАТОЛОГИЙ

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Overlap-Syndrome — A Rare Combination of Three Autoimmune Pathologies

Резюме

Совершенствование методов диагностики и возможностей современной медицины обуславливают более глубокое изучение аутоиммунной патологии. В клинической практике всё чаще стали встречаться случаи сочетанного течения двух и более иммунологических заболеваний, что называют термином «overlap-синдром» или «синдром перекрёста». До сих пор отсутствуют данные о конкретных причинах развития overlap-синдрома, среди наиболее вероятных версий является сочетание генетических изменений, в том числе разнообразия аллелей human leukocyte antigen (HLA), с триггерными факторами извне. Особенности данного синдрома заключаются в трудностях дифференциально-диагностического поиска из-за многообразия симптомов. Несвоевременная верификация диагноза приводит к позднему назначению лечения и менее благоприятному отдалённому прогнозу. В клинической практике наиболее часто встречается сочетание системной склеродермии или системной красной волчанки с ревматоидным артритом. В данной статье приводится пример overlap-синдрома у пациентки 69 лет с тремя аутоиммунными патологиями — системная склеродермия, синдром Шегрена (СШ) и первичный билиарный холангит с полиорганным поражением (лёгкие, кожа, желудочно-кишечный тракт, слюнные железы, сосуды, нервная система). Пациентка имела длительный анамнез синдрома Рейно, а также первичного билиарного холангита. За 2 года до обращения у пациентки был диагностирован синдром Шегрена, в 2025 году — лимитированная форма системной склеродермии. Таким образом, у пациентки в течение жизни развились сразу 3 аутоиммунные патологии, включенные в overlap-синдром. Специалистам следует проявлять повышенное внимание к пациентам с длительным анамнезом ревматологического заболевания для своевременного выявления других аутоиммунных патологий и начала своевременного лечения для предотвращения развития осложнений.

Ключевые слова: *overlap-синдром, синдром перекреста, системная склеродермия, синдром Шегрена, первичный билиарный холангит, прогрессирующий системный склероз*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The improvement of diagnostic methods and the possibilities of modern medicine lead to a deeper study of autoimmune pathology. In clinical practice, cases of a combined course of two or more immunological diseases have become increasingly common, which is called the term "overlap-syndrome" or "crossroads syndrome". There is still no data on the specific causes of the overlap-syndrome, among the most likely versions is a combination of genetic changes, including the diversity of human leukocyte antigen (HLA) alleles, with external trigger factors. The features of this syndrome are the difficulties of differential diagnostic search due to the variety of symptoms. Untimely verification of the diagnosis leads to a late appointment of treatment and a less favorable long-term prognosis. In clinical practice, a combination of systemic scleroderma or systemic lupus erythematosus

with rheumatoid arthritis is most common. This article provides an example of the overlap-syndrome in a 69–year-old patient with three autoimmune pathologies — systemic scleroderma, CABG, and primary biliary cholangitis with multiple organ damage (lungs, skin, gastrointestinal tract, salivary glands, blood vessels, and nervous system). The patient had a long history of Raynaud's syndrome, as well as primary biliary cholangitis. Two years before the treatment, the patient was diagnosed with Sjogren's syndrome, and in 2025, a limited form of systemic scleroderma. Thus, during her lifetime, the patient developed 3 autoimmune pathologies included in the overlap-syndrome. Specialists should pay increased attention to patients with a long history of rheumatological disease in order to detect other autoimmune pathologies in a timely manner and initiate timely treatment to prevent the development of complications.

Key words: *overlap-syndrome, systemic scleroderma, Sjogren's syndrome, primary biliary cholangitis, progressive systemic sclerosis*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
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AMA — antimitochondrial antibodies, ANA — antinuclear antibodies, ACA — anticentromere antibodies, RA — rheumatoid arthritis, SSD — systemic scleroderma, SLI — systemic lupus erythematosus, SS — Sjögren's syndrome, PBC — primary biliary cholangitis

Introduction

Overlap syndrome refers to a group of diseases and clinical conditions that fulfill the classification criteria of two or more immune-mediated inflammatory rheumatic diseases [1]. The development of these systemic autoimmune rheumatic diseases may occur either simultaneously or sequentially, and characteristic immunological abnormalities are not invariably present [2]. The term was first introduced to describe patients with a combined and difficult-to-differentiate clinical presentation of rheumatoid arthritis (RA) together with systemic lupus erythematosus (SLE) or systemic scleroderma (SSD) [3]. The exact cause of the coexistence of multiple rheumatic diseases remains unknown; however, most investigators suggest that overlap syndrome arises from a genetic predisposition triggered by environmental factors. Several studies have highlighted the role of genes within the human leukocyte antigen (HLA) system in the pathogenesis of overlap phenotypes [2]. A characteristic feature of overlap syndrome is the subtle and often attenuated presentation of symptoms, which may result in delayed diagnosis and initiation of treatment, thereby adversely affecting long-term prognosis.

It is important to distinguish overlap syndrome from mixed connective tissue disease. Mixed connective tissue disease is an autoimmune disorder characterised by clinical features of several systemic autoimmune rheumatic diseases in combination with high titers of antibodies directed against soluble nuclear ribonucleoprotein [2]. In clinical practice, however, the differential diagnosis between these conditions may be challenging. Cases of overlap syndromes have been described not only in rheumatology. Well-recognised examples include overlap between respiratory diseases, such as bronchial asthma and chronic obstructive pulmonary disease, as well as gastrointestinal disorders, including autoimmune hepatitis and primary biliary cirrhosis. The true prevalence of overlap syndrome remains uncertain; however, it is estimated to account for up to 20 % of rheumatic diseases [2]. At present, no specific management guidelines exist for this group of patients, and treatment is primarily based on controlling the manifestations driven by the underlying autoimmune process.

Systemic sclerodermas (SSc), also known as progressive systemic sclerosis, is a chronic multisystem disease characterised by a staged course and by vasospastic vascular reactions resembling Raynaud's phenomenon, as well as an obliterative vasculopathy associated with ischaemic tissue injury. The disease is accompanied by specific autoimmune abnormalities that promote fibroblast activation and excessive collagen deposition in tissues, ultimately leading to progressive fibrosis and organ involvement [4]. SSD is associated with the highest mortality among rheumatic diseases [5, 6]. Despite this, early diagnosis of SSD remains challenging because of its highly heterogeneous clinical presentation. Consequently, the correct diagnosis is often established only at advanced stages of the disease, when patients have already developed severe and sometimes life-threatening complications [7]. Antinuclear antibodies (ANA), which are detected in 90–95 % of patients, are commonly used

as diagnostic markers of SSD; however, these antibodies are not disease-specific and may also be present in a variety of other pathological conditions. Less specific markers include anticentromere antibodies (ACA) and anti-topoisomerase I antibodies (anti-Scl-70), which are detected in approximately 60 % of patients, particularly among those with cardiopulmonary complications. Antibodies against RNA polymerase III are identified less frequently, mainly in patients with diffuse systemic scleroderma, and are associated with the development of scleroderma renal crisis, a form of acute kidney injury [8]. In addition, several autoantibodies have been described in approximately 10 % of patients who are seronegative for the classical markers. These include anti-eIF2B antibodies, the anti-RuvBL1/2 complex, anti-U11/U12 RNP antibodies, and anti-BICD2 antibodies [9].

Sjögren's syndrome (SS) is an autoimmune disease of unknown etiology characterised predominantly by involvement of the salivary and lacrimal glands, resulting in dry mouth (xerostomia) and dry eyes (xerophthalmia), with possible involvement of the respiratory tract, gastrointestinal tract, and vagina. SS can be primary or secondary. Primary SS develops independently and is not associated with other diseases, whereas secondary SS occurs in patients with an underlying rheumatic disorder, such as SLI, RA or SSD [9]. The association between SS and SSD is thought to be related to the presence of anticentromere antibodies. In such cases, Raynaud's phenomenon is a common manifestation of SS [10].

Primary biliary cholangitis (PBC) is a rare chronic autoimmune cholestatic liver disease characterised by T-lymphocyte-mediated injury of the intrahepatic biliary epithelial cells, which may ultimately lead to liver cirrhosis. A distinctive feature of PBC is its frequent association with other autoimmune diseases and syndromes [11]. Detection of antimitochondrial antibodies (AMA), directed against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) located on mitochondrial membranes, represents a highly specific diagnostic marker of the disease [11]. PBC most commonly coexists with autoimmune hepatitis, whereas the prevalence of concomitant PBC and SSD occurs in only 2–4 % of cases [12].

A search of the PubMed database covering the period from 1993 to 2025 using the terms "systemic scleroderma, Sjögren's syndrome, primary biliary cholangitis overlap syndrome" yielded 14 records. However, none of the retrieved publications described cases involving the coexistence of all three conditions simultaneously. In the present article, we describe a clinical case of a patient with an overlap syndrome comprising the coexistence of all three aforementioned conditions, i.e., systemic scleroderma, Sjögren's syndrome, and primary biliary cholangitis with multisystem organ involvement.

Clinical Case Report

A 69-year-old woman was admitted to the rheumatology department in May 2025 with complaints of dry mouth and dry eyes, skin dryness, pruritus, muscle cramps affecting both the upper and lower extremities, and dysphagia manifested by difficulty swallowing dry food. In addition, the patient had recently begun to experience exertional dyspnea of mixed origin and an occasional dry cough during routine physical activity. Two days prior to admission, she reported a single episode of hemoptysis and the appearance of black stools.

On admission, the patient was in a moderately severe condition. The skin was of normal colour but appeared indurated on palpation, with excoriations present on both the upper and lower extremities and reduced skin turgor. Physical examination revealed bilateral Dupuytren's contractures, characteristic perioral tightening with a "purse-string" appearance of the mouth, palmar capillaritis, and telangiectasias on the anterior chest wall. The modified G.P. Rodnan skin score was 2 points, indicating moderate skin thickening, with the skin being difficult to lift into a fold. Pulmonary examination revealed harsh breath sounds with a respiratory rate of 18 breaths per minute and SpO_2 saturation of 98 %. Breath sounds were present throughout both lungs, and fine inspiratory crackles were auscultated bilaterally at the lung bases up to the level of the inferior angles of the scapulae. Heart sounds were muffled, rhythm was regular, and no murmurs were detected. Blood pressure was 120/80 mm Hg, and heart rate was 68 beats per minute. The tongue was dry and moderately coated with a yellowish deposit at the root. The abdomen was soft and non-tender on palpation, with no signs of peritoneal irritation. On percussion, the liver did not extend below the costal margin; however, palpation revealed a nodular, firm, and painless lower liver edge.

According to the medical history, Raynaud's phenomenon was diagnosed in 1984. In 2023, following the onset of xerostomia and xerophthalmia, the patient underwent further evaluation and was diagnosed with Sjögren's syndrome by a rheumatologist. The diagnosis was based on characteristic symptoms, a positive ANA test, elevated anti-LA/SS-B antibody levels (>200 U/mL; reference range 0–15 U/mL), as well as findings from sialography, sialometry, and salivary gland biopsy. The patient also had a confirmed diagnosis of PBC, which had progressed to Child-Pugh class B subcompensated liver cirrhosis. AMA were positive in February 2025. The disease was complicated by intrahepatic portal hypertension with esophageal and gastric varices and recurrent episodes of upper gastrointestinal bleeding. The patient has been receiving long-term therapy with calcium and vitamin D supplements, denosumab according to the prescribed regimen, spironolactone 50 mg daily, ursodeoxycholic acid 500 mg twice daily, L-ornithine

L-aspartate 3 g daily, and methylprednisolone 4 mg daily. The patient repeatedly refused treatment with hydroxychloroquine. A timeline of the patient's medical history is presented in Figure 1.

Laboratory investigations performed during hospitalisation revealed normochromic normocytic anaemia, with a haemoglobin level of 72 g/L (reference range: 120–140 g/L), decreased hematocrit of 28.1 % (35–47 %), thrombocytopenia with a platelet count of 135 × 10^9/L (180–320 × 10^9/L), whereas the white blood cell count was within the normal range at 7.64 × 10^9/L (5–9 × 10^9/L). Liver transaminase levels were within the reference range. Immunological testing demonstrated a positive antinuclear factor (ANF) titer of 1:640 (reference value <1:160) and positive ACA.

Computed tomography (CT) of the chest showed signs of bronchiolitis. Echocardiography revealed normal systolic and mean pulmonary artery pressures.

Abdominal ultrasonography demonstrated a moderate amount of free intraperitoneal fluid, diffuse cirrhotic changes of the liver, reactive oedema of the perivesicular tissue, and diffuse changes of the pancreas.

Ultrasonography of the parotid and submandibular salivary glands demonstrated diffuse changes characterised by moderately heterogeneous glandular architecture and reduced vascularisation of the parenchyma.

Esophagogastroduodenoscopy (EGD) revealed grade III esophageal varices according to the Sherzinger classification, as well as gastric varices (GOV1/GOV2 according to the Sarin classification). In addition, erosive reflux esophagitis was observed, with edematous esophageal mucosa and linear erosions covered with fibrin deposits involving all walls of the esophagus. Multiple flat erosions measuring up to 0.3 cm in diameter and covered with fibrin were present throughout the antrum of the stomach, while flat elevated hyperplastic lesions were identified in the gastric fundus. Liver elastography demonstrated stage F4 fibrosis according to the METAVIR scoring system.

Given the long-standing history of Raynaud's phenomenon, capillaroscopy was performed. The examination revealed an irregular arrangement of capillaries with dilated loops, reduced capillary density, and extensive avascular areas.

Thus, taking into account the presence of bronchiolitis, Raynaud's phenomenon, and cutaneous manifestations (indurative skin edema and a characteristic "purse-string" appearance of the mouth), together with positive immunological markers, the patient was diagnosed with SSD within the framework of an overlap syndrome comprising systemic scleroderma, primary biliary cholangitis, and Sjögren's syndrome (SSD + PBC + SS).

The diagnosis of SSD was established according to the current classification criteria (Table 1) of ACR/EULAR (American College of Rheumatology/European League Against Rheumatism Systemic Sclerosis classification criteria).

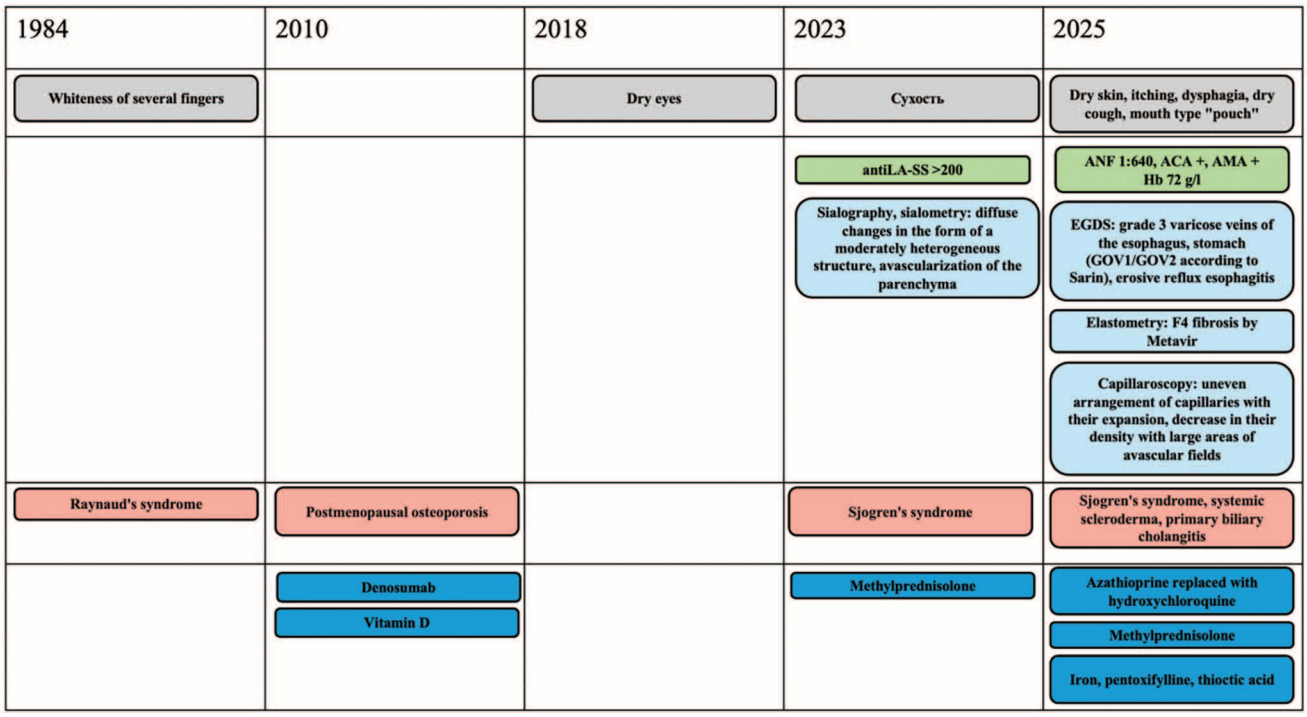

Figure 1. *Medical history of the patient*

Abbreviations shown in the figure: ANF — antinuclear factor, ACA — anticenter antibodies, AMA — antimitochondrial antibodies, EGDS — esophagogastroduodenoscopy, Hb — hemoglobin

Table 1. *Classification criteria of the 2013 ACR/EULAR SSD*

Parameter	Signs	Scores
Thickening of the skin of the fingers of both hands, extending proximally to the metacarpal joints (sufficient criterion)	-	9
Thickening of the skin of the fingers (only the maximum score is taken into account)	Dense swelling of the fingers	2
	Sclerodactyly (distal to the metacarpophalangeal joints)	4
Fingertip changes (only the maximum score is taken into account)	Ulcers of the fingertips	2
	Scarring on the fingertips	3
Telangiectasia	-	2
Changes in capillaries of the footbed	-	2
Pulmonary arterial hypertension and/or interstitial lung disease	Increased pressure in the pulmonary artery according to EchoCG data	2
	Signs of interstitial lung damage according to CT	2
The Raynaud phenomenon	-	3
Autoantibodies characteristic of SSD	Anti-centromeric	3
	Antibodies to topoisomerase I	3
	Antibodies to RNA polymerase III	3
Total		23 из 30

Note. 9 points or more is a diagnosis of reliable SSD. The criteria available to this patient are highlighted in color.
Abbreviations in the table: EchoCG- echocardiography, CT — computed tomography, RNA — ribonucleic acid, SSD — systemic scleroderma

Clinical diagnosis:

Primary diagnosis: overlap syndrome. Limited systemic scleroderma, chronic course, with involvement of the lungs (bronchiolitis), vasculature (Raynaud's phenomenon, capillaroscopic abnormalities, telangiectasias), gastrointestinal tract (esophageal hypomotility), skin (sclerodactyly with puffy fingers; modified G.P. Rodnan skin score of 2 points), nervous system (polyneuropathy), and immunological abnormalities (positive ANF and ACA). Sjögren's syndrome with involvement of the lacrimal glands (xerophthalmia, dry keratoconjunctivitis), salivary glands (chronic parenchymal parotitis, grade 3 xerostomia), and immunological abnormalities (positive ANF). Primary biliary cholangitis with progression to liver cirrhosis, Child-Pugh class B, with positive AMA-M2.

Complications: portal hypertension; grade III esophageal varices according to the Sherzinger classification; gastric varices (GOV1/GOV2 according to the Sarin classification); portal hypertensive gastropathy; hypersplenism syndrome with latent thrombocytopenia; grade I hepatic encephalopathy; and moderate normochromic normocytic anemia.

Comorbidities: chronic non-atrophic Helicobacter pylori-negative gastritis; gallbladder polyp; hepatic cyst; postmenopausal osteoporosis (T-score = −3.1), with a 10-year probability of osteoporotic fractures of 11.6% according to the FRAX tool.

Given the coexistence of three autoimmune diseases, initiation of azathioprine therapy at a dose of 50 mg/day with subsequent dose titration was recommended. Continuation of methylprednisolone at a dose of 4 mg/day was advised, together with the addition of iron supplementation, thioctic acid, and pentoxifylline.

In June 2025, azathioprine was replaced with hydroxychloroquine at a dose of 200 mg/day because of generalised weakness and loss of appetite. At follow-up in September 2025, the patient reported satisfactory well-being, with regression of muscle cramps, pruritus, and dyspnea. Biochemical blood tests performed in September 2025 demonstrated a slight elevation of alanine aminotransferase to 40.5 U/L (reference range 0–34 U/L), aspartate aminotransferase to 34.5 U/L, and gamma-glutamyl transferase to 56.4 U/L.

Discussion

Despite the fact that the diagnosis of autoimmune diseases has been greatly facilitated by the availability of serological testing for a wide range of autoantibodies, the identification of overlap syndromes remains challenging because of the distinctive features of their onset and clinical course.

The pathogenic mechanisms underlying the coexistence of multiple autoimmune diseases are not fully understood. It has been suggested that defects in immune regulation associated with genetic polymorphisms and environmental factors play a key role in their development.

SS is frequently associated with other rheumatic diseases. According to a retrospective study, among 1,119 patients with SS, 308 (27.5 %) were diagnosed with PBC [13].

The coexistence of three autoimmune diseases is uncommon. Date K. et al. reported a case of acute phlegmonous esophagitis caused by Candida spp. in a patient with SS, primary biliary cholangitis, and autoimmune hepatitis [14]. This case highlighted the importance of close monitoring of patients with multiple autoimmune disorders and regular assessment of laboratory parameters to prevent infectious complications, which may arise due to immune dysfunction.

Han H.S. et al. described a patient with PBC and autoimmune hepatitis who subsequently developed SSD. The authors emphasised the common pathogenetic background shared by these diseases [15].

Iikuni N. et al. reported a patient with SSD and SS who later developed primary biliary cirrhosis and Graves' disease [16]. In contrast to the present case, our patient initially developed SS and PBC, with manifestations of SSD appearing later in the disease course. No previous reports describing the coexistence of these three autoimmune diseases have been published. This observation further underscores the importance of extending the diagnostic workup in patients with an already established autoimmune disease, particularly when new clinical manifestations emerge.

Conclusion

A distinctive feature of overlap syndrome is the ability of each autoimmune disease to modify the clinical manifestations of the others, which considerably complicates timely diagnosis and appropriate treatment. Therefore, clinicians should remain aware of the heterogeneous nature of autoimmune disorders and consider the possibility of an overlap syndrome in patients.

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Яровой М.Д.: написание статьи, анализ клинического случая, обзор литературы, перевод на английский язык

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Iarovoi M.D.: article writing, literature review, case study analysis, translation into English

Khachirova E.A.: case study selection, selection and processing of the visual materials, text editing.

V.S. Shemenkova: article writing, text editing

Reznik E.V.: idea, leadership, work organization, edition

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