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(CASE REPORT)

Complex connective tissue convergence: A case report of scleroderma, systemic lupus erythematosus, and Sjögren's Syndrome overlap syndrome in an adolescent female

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Abstract

This case report illustrates the uncommon occurrence of an overlap syndrome involving systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and Sjögren's syndrome in a 16-year-old female patient. Despite their distinct pathophysiological mechanisms and clinical manifestations, these connective tissue diseases converged in this patient, presenting a diagnostic challenge. The clinical presentation included features such as Raynaud's phenomenon, mouth and digit ulcers, alopecia, photosensitivity, and positive autoantibodies. Diagnostic workup revealed positive findings on antinuclear antibodies (ANA) and extractable nuclear antigen (ENA) panel, confirming the presence of autoantibodies associated with all three conditions. The patient was managed with a combination of symptomatic treatment, hydroxychloroquine, and prednisolone. This case underscores the complexity of overlapping autoimmune diseases and emphasizes the importance of a thorough clinical evaluation, appropriate diagnostic testing, and timely initiation of management to optimize patient outcomes.

Keywords: Overlap Syndrome; Connective Tissue Diseases; Scleroderma; systemic lupus erythematosus; Sjögren's syndrome; Complex connective tissue convergence

1. Introduction

Autoimmune conditions are intricate and typically not very common. Distinctive indications, manifestations, and autoantibodies help identify particular connective tissue diseases. Some individuals meet criteria for more than one defined connective tissue disease (CTD), while others exhibit various symptoms typical of autoimmune diseases without a clear diagnosis.[1]

Presently, there are established criteria for categorizing five distinct autoimmune connective tissue diseases: Systemic lupus erythematosus (SLE), scleroderma, myositis, rheumatoid arthritis (RA), and Sjogren's syndrome. While each of these conditions varies in its presentation, typically, a clear diagnosis of a defined connective tissue disease (CTD) becomes evident with time. However, some individuals may exhibit features common to autoimmune diseases, such as Raynaud's phenomenon (RP), joint pain, muscle pain, or a positive anti-nuclear antibody (ANA) test, without meeting the criteria for a specific condition. In such instances, arriving at a diagnosis may be less straightforward, and these

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patients are often labeled as having undifferentiated connective tissue disease "UCTD." Additionally, some individuals may fulfill criteria for two or more distinct autoimmune conditions, leading to what is known as an "overlap syndrome."[1]

Overlap syndromes are typically characterized by meeting the criteria for multiple traditional autoimmune connective tissue diseases (CTDs). Patients might show indications of more than one illness concurrently or develop different illnesses in succession. Some individuals might display two or more diseases with specific blood markers for those conditions. It can be beneficial to classify patients according to patterns of clinical characteristics. Researchers have examined cohorts of patients with comparable overlap clinical features over time and pinpointed distinct autoantibodies, aiding in refining certain overlap syndromes.[1]

Systemic sclerosis (SSc) is an autoimmune disorder marked by the buildup of collagen in various tissues, leading to damage in multiple organs and impaired function. SSc exhibits variability, not only evident in limited and diffuse skin lesions, but also in the range of organs affected.

This result is notable distinctions in the pattern, severity, progression, mortality, and treatment options for organ damage among patients.[2]

[3] Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple systems, characterized by periods of flare-ups and remissions. While the precise cause of this condition remains unclear, research indicates that a combination of genetic and environmental factors triggers abnormal immune responses, resulting in the production of harmful autoantibodies by B cells and dysregulation of cytokines, ultimately leading to damage in tissues and organs. SLE is distinguished by the presence of antibodies targeting nuclear and cytoplasmic antigens. It presents a wide range of clinical manifestations, from mild skin involvement to severe organ complications such as renal failure, pulmonary hypertension, and cardiac dysfunction.[3]

Sjögren syndrome is a chronic autoimmune disorder characterized by infiltration of lymphocytes into the exocrine glands, particularly the salivary and lacrimal glands, along with heightened B-cell activity. While traditionally viewed as primarily affecting these glands, resulting in symptoms such as dry mouth and eyes, it also presents various systemic manifestations affecting virtually any organ system. In rare cases, it can lead to the development of non-Hodgkin lymphoma. Secondary Sjögren syndrome is linked with an existing connective tissue disease.[4]

We present a case of a 16-year-old girl, who presented with a unique combination of three connective tissue disease: Scleroderma, Systemic lupus erythematosus, and Sjogren syndrome.

2. Case presentation

A 16-year-old girl with a medical history significant for treated pulmonary tuberculosis presented to our tertiary care hospital with a constellation of symptoms spanning several months. She reported experiencing bluish discoloration of her fingers for the past 6 months, accompanied by persistent dryness of the mouth, eyes, and joint pain for 3 months. Additionally, she complained of mouth and digit ulcers persisting for 2 months, alopecia, and difficulty in swallowing for the same duration. Over the past month, she had developed a low-grade fever, shortness of breath, increased urinary frequency over 3 weeks, and generalized body swelling progressing over 1 week.

Upon vital assessment, her blood pressure measured 110/70 mmHg, pulse rate was elevated at 102 beats per minute, and oxygen saturation was 97% on room air. Her respiratory rate was within normal limits at 20 breaths per minute. General physical examination revealed an anemic appearance, edema, and palpable lymph nodes in the left anterior cervical region. The Renold phenomenon was positive. Notable findings included mouth ulcers, finger and toe ulcers (**shown in figure 1a & 1b**) alopecia, photosensitivity, and a positive malar rash (**shown in the figure 2**)

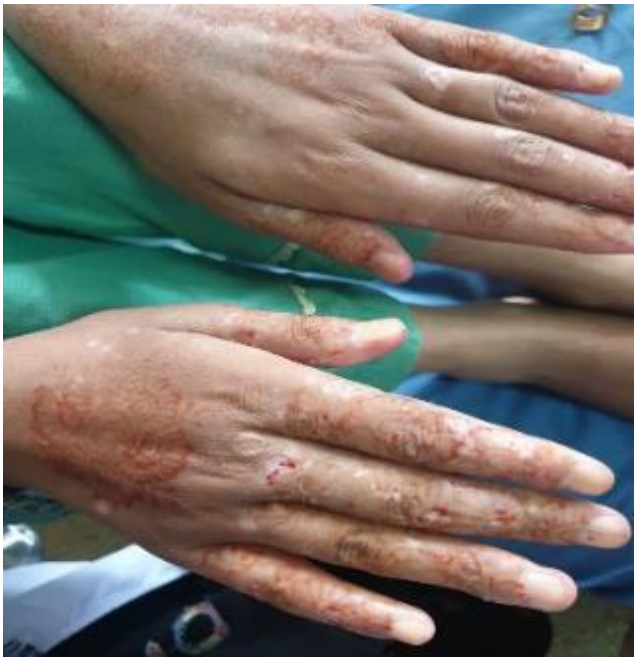

Figure 1a Fingers ulcers

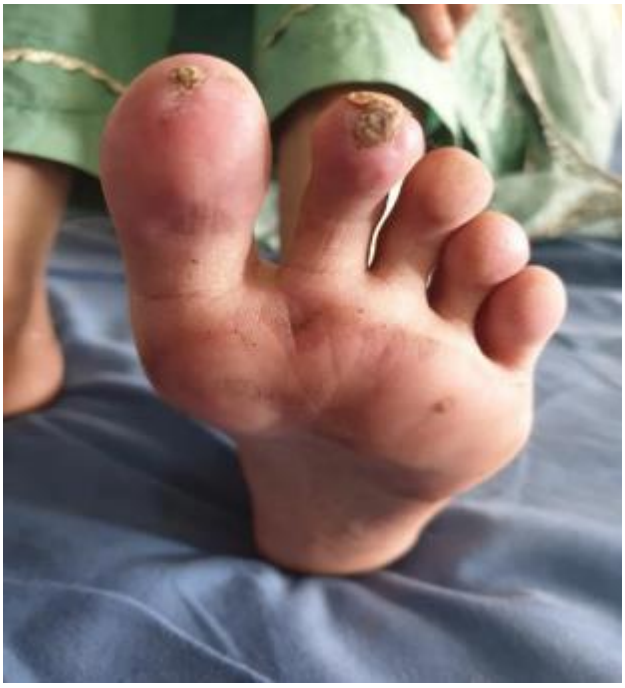

Figure 1b Toe ulcers

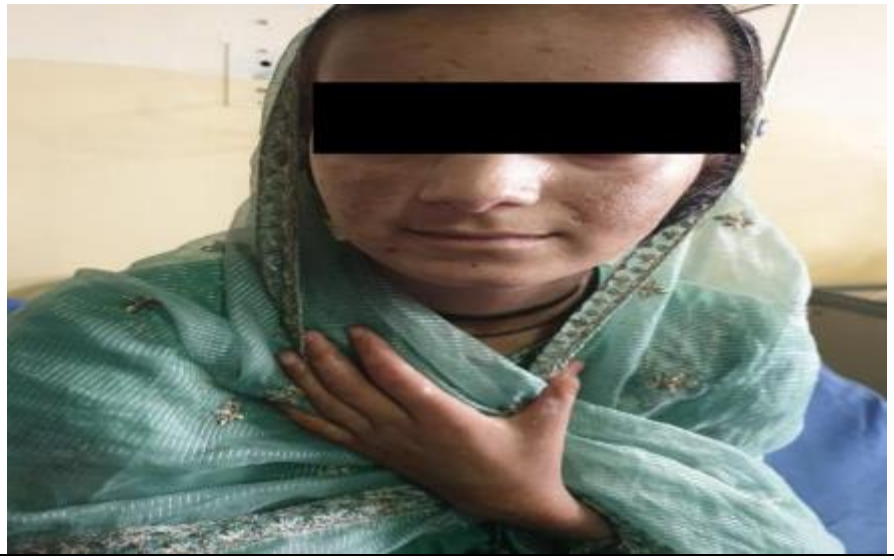

Figure 2 Malar Rash

Systemic examination revealed basal crepitations bilaterally in the chest, while the abdomen was soft, non-tender, and mildly distended. Other examinations were unremarkable.

Basal laboratory investigations along with antinuclear antibodies (ANA) were conducted, demonstrating decreased hemoglobin and platelets, increased total leukocyte count (TLC), and deranged renal function tests (RFTs). The ANA test was strongly positive, and the reticulocyte count was elevated at 2.9%. The urine protein/creatinine ratio was elevated at 0.5 (normal range < 0.2), with decreased C3 levels (0.21 g/L; normal range 0.9-1.8 g/L) and decreased C4 levels (0.02 g/L; normal range 0.1-0.4 g/L). Subsequently, an extractable nuclear antigen (ENA) panel was sent for further evaluation of autoimmune disease, revealing positive results for anti-double-stranded DNA (dsDNA) IgG (61.0 IU/ml; positive > 30), Sm antibodies (9.8 U/ml; positive > 5.0), SS-A/Ro antibodies (7 U/ml; positive > 5.0), SS-B/La antibodies (19.8 U/ml; positive > 12.5), and Scl-70 antibodies (48.29 U/ml; positive > 5.0), while testing negative for U1-RNP, Anti-Mi-2 and Anti-Jo-1 antibodies. The Schirmer test for ocular dryness was also positive. A biopsy of the kidney was recommended but declined by the patient's mother.

Based on the clinical presentation and diagnostic findings, the patient was diagnosed with an overlap syndrome of Systemic Lupus Erythematosus (SLE), Scleroderma, and Sjogren's Syndrome. She was initiated on symptomatic management along with Hydroxychloroquine (HCQ) 200 mg orally once daily and deltacortril (prednisolone) 5 mg continuously. The patient and her family were counseled regarding the disease course, potential complications, and the importance of medication adherence. She was discharged with plans for regular follow-up as an outpatient to monitor disease progression and treatment response.

3. Discussion

Connective tissue disorders are a range of disorders that primarily affect the joints, muscles and skin but can include other organs as well including the heart, brain, eyes and liver.[5] The major connective tissue diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome, scleroderma and myositis.[6] Our patient presented with the features of scleroderma, Sjögren's syndrome and systemic lupus erythematosus.

Mixed connective tissue disorder is a rare autoimmune disease in which a patient has features of two or more connective tissue diseases including scleroderma, Sjögren's syndrome, SLE, polymyositis or dermatomyositis.[6] One of the commonly used diagnostic criteria for MCTD is Alarcon-Segovia criteria which requires a high titers of anti U1-RNP and three or more of the clinical the following clinical features: Raynaud's phenomenon, hand edema, synovitis, myositis, and acrosclerosis.[7] Our patient has the clinical features of MCTD including Raynaud's phenomenon, hand edema, synovitis and acrosclerosis, but has a negative anti U1-RNP which rules out MCTD. MCTD is one type of overlap syndrome which is the presence of two or more connective tissue diseases in the same patient.[8] A patient should have a positive anti U1-RNP, which our patient lacks, to be diagnosed as MTCD as it is the characteristic feature of MCTD.[6] Thus our patient has the overlap syndrome but not MCTD. A large percentage of patients with overlap syndrome have features of inflammatory myopathies.[9] In contrast, our patient lacked features of polymyositis or dermatomyositis. Our case was diagnosed as overlap syndrome of Systemic Lupus Erythematosus, Sjogren's syndrome and Scleroderma which is a rare combination of connective tissue illnesses in a patient.

In our case, the patient also had microcytic anemia with hemoglobin of 8.1 g/dL and MCV of 65.6. This could be due to a variety of reasons including decreased intake in diet which is common in Pakistan or due to gut sclerosis decreasing nutrient absorption secondary to scleroderma.[15] In addition, our patient tested positive for anti Scl-70. Both anemia and anti Scl-70 are associated with increased risk of worsening organ damage in patients with systemic sclerosis.[2]

4. Conclusion

The presented case exemplifies the intricate nature of autoimmune connective tissue diseases and the possibility of overlap syndromes manifesting in clinical practice. Despite the rarity of such occurrences, clinicians should remain vigilant in recognizing overlapping features across different autoimmune conditions, as prompt diagnosis and intervention are crucial for improving patient prognosis. Additionally, this case highlights the significance of interdisciplinary collaboration and regular follow-up care to effectively manage complex autoimmune presentations and mitigate the risk of complications. Further research and accumulation of similar cases are warranted to enhance our understanding of overlap syndromes and refine treatment strategies tailored to individual patient needs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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Authors short Biography

Kamran Ahmad, MD, a dedicated medical doctor hailing from Pakistan, possesses a profound interest in research. With a commitment to advancing medical knowledge, he actively contributes to the exploration of healthcare innovations and solutions