Case Report

A Case of Scleroderma-systemic Lupus Erythematosus Overlap Syndrome in a 22-Year-Old Filipino Female

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Abstract

Overlap syndrome is a rare condition involving the coexistence of at least two distinct autoimmune diseases, such as systemic lupus erythematosus and systemic sclerosis. This condition has limited studies on epidemiology probably because it is often under-recognized. We present a 22-year-old Filipino female with a 10-month history of hyperpigmented patches on the malar surface and extremities, with associated photosensitivity, fatigue, pallor, arthralgia, and oral ulcers, and positive antinuclear antibody titer. She was treated with oral Prednisone in tapering doses, leading to clinical improvement. Eight months later, there was a recurrence of hyperpigmented patches on the face and extremities with skin tightening and diffuse hair loss, development of shiny skin with facial fold loss, a beak-like nasal appearance, and episodes of dyspnea and malaise. Consistent with scleroderma, the patient was started on mycophenolate mofetil (MMF) 500 mg daily, with close monitoring for disease progression and systemic involvement. Overlap syndrome remains under-recognized due to its variable presentation and rarity. Treatment is individualized based on the specific connective tissue diseases involved and the patient's symptoms. Multidisciplinary care is crucial for timely management and to adjust treatment as needed, given the potential for life-threatening complications involving cutaneous and internal organs.

Keywords: Histopathology, overlap syndrome, systemic lupus erythematosus, systemic sclerosis

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Introduction

Overlap syndrome is a rare condition characterized by the coexistence of clinical and immunological features of two or more autoimmune connective tissue diseases, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome, and others. The co-occurrence of SLE and SSc presents significant diagnostic and therapeutic challenges. Patients with SLE-SSc overlap syndrome are typically younger, with a notable female predominance.[1] Symptoms are highly variable, ranging from skin manifestations to systemic involvement, and the condition is often underdiagnosed due to the subtle overlap of symptoms. Studies indicate that the prevalence of the SLE-SSc overlap is approximately 6.8% among patients with SSc.[1] Pharmacological therapeutic options primarily include corticosteroids, disease-modifying antirheumatic drugs (DMARDs), synthetic or biological, and immunosuppressive drugs. Biologic therapies, such as anti-tumor necrosis factor-alpha or anti-CD20 monoclonal antibodies, have been used as alternative treatments in refractory cases.[2] Here, we present a case of a 22-year-old Filipino female with SLE-SSc overlap

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syndrome, highlighting the importance of maintaining a high index of suspicion and the need for early intervention to prevent disease progression.

Case Report

A 22-year-old Filipino female presented with a 10-month history of multiple hyperpigmented patches over the malar area and extremities, accompanied by photosensitivity, easy fatigability, pallor, joint pains, and recurrent oral ulcers. She sought consultation and was subsequently diagnosed with SLE based on her clinical features and a positive antinuclear antibody (ANA) test. The patient was started on prednisone, which was tapered accordingly, resulting in clinical improvement.

Eight months after the resolution of symptoms, she developed diffuse hair loss, progressive skin tightening, and recurrence of hyperpigmented facial patches. No medical consultation was sought at that time.

In the interim, there was noted progression of symptoms. She experienced dyspnea and malaise, along with the appearance of multiple well-demarcated, some targetoid, erythematous to hyperpigmented patches and plaques with overlying crusts on the palms, fingertips, and soles. The patient also noted a shiny skin with a loss of normal facial folds and a beaked nasal appearance. The persistence of lesions with the progression of dyspnea and malaise prompted consult and subsequent hospital admission.

Past medical history revealed that the patient was diagnosed with nephrotic syndrome when the patient was 16 years old. Family history was unremarkable. The patient is a college student with no vices, living with her family.

A review of systems showed thinning of hair and stiffness of fingers with occasional pain.

The patient was conscious, coherent, and in cardiorespiratory distress with the following vital signs: blood pressure of 110/80; CR of 107; respiratory rate of 30; Temp of 37.9 C. Physical examination showed a mask-like facie with stretched, shiny skin with loss of normal facial folds, beak-like sharp nose; multiple, clear fluid-filled vesicles over the trunk and both upper extremities; generalized, well-defined hypo-and hyperpigmented macules and patches with erosions and ulcers over the back (salt and pepper lesions); multiple, well-defined, some targetoid, erythematous to hyperpigmented patches and plaques with crusts over the palms, fingertips, and soles; several, ill-defined, white patches over the lateral aspects of the tongue [Figure 1].

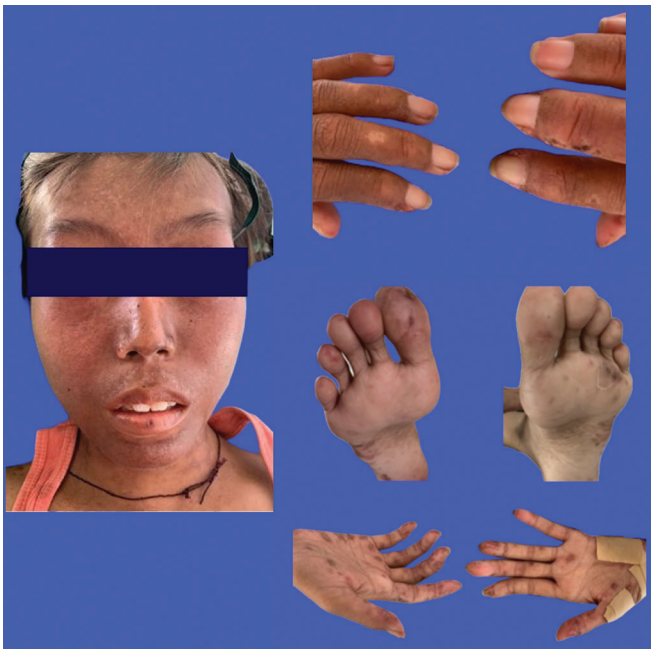


Figure 1: Leftmost: Clinical photo showing a mask-like facie and a beak-shaped nose; rightmost: Note the puffy fingers and fingertip pitting scars

Complete blood count shows leukocytosis, lymphophenia, and anemia. Serum chemistries revealed high creatinine levels (117). Urinalysis showed blood hematuria, proteinuria, pyuria, and presence of red blood cells protein. Due to financial constraints, anti-dsDNA and Anti-centromere Ab were not done. Syphilis test was requested with a nonreactive result. Plain computed tomography (CT) scan showed minimal pleural effusion. A 4 mm skin punch biopsy was performed with results consistent with a mixed connective tissue disease (lupus erythematosus scleroderma). Histopathology report showed a basket-woven orthokeratosis with moderately dense superficial and mid-perivascular and peri-adnexal infiltrates of histiocytes, telangiectatic blood vessels, and scattered blue-gray granules in the upper dermis and focal thickening of collagen bundles in the lower dermis consistent with scleroderma and lupus erythematosus [Figure 2].

The patient was managed as a case of overlap syndrome scleroderma SLE, fulfilling the following criteria in the diagnosis of scleroderma as shown in Table 1, as well as the following criteria in the diagnosis of SLE as shown in Table 2.

Patient was managed with clindamycin 600 mg TIV Q8, hydrocortisone 100 mg TIV OD, MMF 500 mg/tablet 1 tablet BID, mupirocin ointment BID, and was transfused with 2 units of packed RBC. The patient was discharged against medical advice.

Table 1: Criteria for systemic scleroderma

Systemic scleroderma criteria (2013 ACR/EULAR criteria for the classification of systemic sclerosis[5])			
Criteria	**Subset criteria**	**Weight/score**	**Patient's score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9	-
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2	
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal phalangeal joints)	4	4
Finger tip lesions (only count the higher score)	Digital tip ulcers	2	
	Fingertip pitting scars	3	3
Telangiectasia	-	2	-
Abnormal nailfold capillaries	-	2	-
Pulmonary hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2	
	Interstitial lung disease	2	2
Raynaud's phenomenon	-	3	-
Ssc-related autoantibodies [anti-centromere, anti-topoisomerase I (anti-Scl70), anti-RNA polymerase III] (maximum score 3)	Anticentromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3	-
Total: The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of >9 are classified as having definite SSc[3]			9

Source: Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, *et al*. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2013;65:2737-47.[5] SSc: Systemic sclerosis

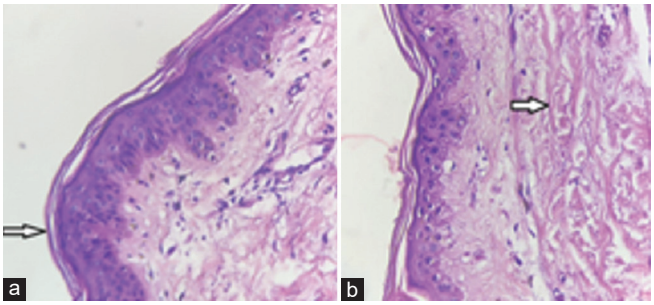


Figure 2: The arrows highlight the basket-woven stratum corneum (a) and thickening of collagen bundles (b). At 200x magnification

Discussion

Overlap syndrome is a disease entity manifesting with symptoms and satisfying the criteria of two or more from two or more autoimmune or connective tissue diseases such as SLE, scleroderma, Sjogren syndrome, polyarthritis, vasculitis, and dermatomyositis. Among these diseases, the majority of the diagnosis derives from the fusion of features of SLE and SSC.[3]

In this case, the patient initially presented with clinical features suggestive of SLE, including malar rash, photosensitivity, anemia, and a positive ANA result, fulfilling the 1982 Revised Criteria for Classification of SLE.[4] Over time, she developed signs and symptoms consistent with SSc (scleroderma), suggesting an overlap syndrome.

Scleroderma typically begins with skin involvement in the hands and fingers, which is a cardinal feature. This is followed by the development of nonpitting edema of the fingers, hands, and extremities with progressive skin thickening (sclerodactyly). In the present case, the patient developed skin thickening of the fingers, fingertip pitting scars, and pleural effusion, further supporting the diagnosis of an SLE-SSc overlap.

The 2013 ACR/EULAR criteria for the classification of SSc[5] is commonly used to establish the diagnosis of scleroderma based on the organ involvement. For skin involvement, the modified Rodnan skin score is used to assess skin thickness [Figure 3]. Seventeen body sites are evaluated, and the degree of skin thickening is graded from 0 to 3, corresponding to no thickening (0), mild (1), moderate (2), and severe thickening (3), based on the skin palpation of a trained examiner.[6]

This figure shows the areas of involvement fulfilled by the patient [Figure 3].

For musculoskeletal involvement, laboratory parameters such as erythrocyte sedimentation rate, rheumatoid factor, and ANA can be requested. For the patient presented, ANA was done with a positive result. Radiography, such as X-ray or high-resolution CT scan, is requested to note for respiratory involvement like interstitial lung disease. The patient was noted to have minimal pleural effusion on a plain CT scan. Kidney function tests and liver enzymes may be requested to note for kidney involvement. The patient was noted to have high creatinine with a result of 117 μmol/L.

There was no specific serological marker identified yet for scleroderma, but a high incidence of anti-dsDNA

Table 2: Criteria for systemic lupus erythematosus

Systemic lupus erythematosus criteria (the 1982 revised criteria for classification of systemic lupus erythematosus[4])			
Criteria	**Definition**	**Weight/score**	**Patient's score**
Malar rash	Fixed erythema, flat or raise, over the malar eminences	1	1
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur	1	-
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation	1	1
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician	1	-
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion	1	1
Serositis	Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion Or Pericarditis – documented by electrocardiogram or rub evidence of pericardial effusion	1	-
Renal disorder	Persistent proteinuria - >0.5 g/day or greater than 3+ if quantitation not performed Or Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed	1	-
Neurologic disorder	Seizures – in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance) Or Psychosis – in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)	1	-
Hematologic disorder	Hemolytic anemia – with reticulocytosis Or Leukopenia - <4000 uL total on 2 or more occasions Or Lymphopenia - <1500/μL on 2 or more occasions Or Thrombocytopenia - <100,000 μL in the absence of offending drugs	1	1
Immunologic disorder	Anti-DNA - antibody to native DNA in abnormal titer Or Anti-Smith antigen – presence of antibody to Smith nuclear antigen Or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of immunoglobulin G or immunoglobulin M anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for atleast 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	1	-
ANA	An abnormal titer of ANA by immunofluorescence of an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome	1	1
Total: Four of the 11 criteria are needed for the formal diagnosis of SLE			5/11

Source: Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7, copyright 1982, with permission of the American College of Rheumatology.[4] SLE: Systemic lupus erythematosus, ANA: Antinuclear antibody

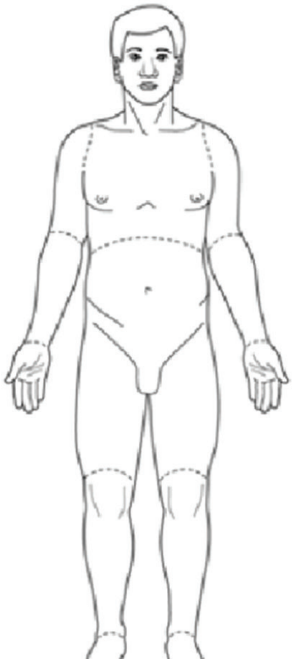
and anti-Scl70 antibodies has been reported.[7] Common antibodies or immune proteins in lupus are anti-dsDNA, anti-smith, anti-Ro/SSB, and anti-LaSSB. However, these laboratory tests were not facilitated due to lack of funds.

There is currently no cure for either lupus or scleroderma, but therapies help to manage both conditions.[5] Treatment depends on the associated connective tissue disease, and they may react differently to therapies; therefore, it should be individualized.

Pulmonary hypertension in SLE patients inflicts a rapid commencement of immunosuppression among patients on cytotoxic drugs and glucocorticoids. However, high doses of glucocorticoids in SLE may be limited by the concomitant SSc-diffuse form potentiating renal crisis, requiring early use of cytotoxic drugs.

Skin involvement is managed with physical therapy and regular exercise to maintain circulation, muscle strength, and joint mobility. Topical medications can be used are steroids, calcineurin inhibitors, and moisturizing cremes. Phototherapy (ultraviolet A1 or psoralen and ultraviolet A) appears to inhibit fibrotic and inflammatory processes and reduce the amount of sclerotic skin.[2]

General immunosuppression can improve skin involvement and interstitial lung disease. The best evidence is available for cyclophosphamide but MMF has been shown to be as effective as oral cyclophosphamide and is used by many centers.[1] Dosing can be increased up to 3 g daily depending on the patient's tolerability.[8] The patient was started on MMF 500 mg daily due to its better safety profile, tolerability, and easier administration than cyclophosphamide. Other immune suppressants may also



	Right				Left			
Fingers	0☐	1☐	2■	3☐	0☐	1☐	2■	3☐
Hands	0☐	1☐	2■	3☐	0☐	1☐	2■	3☐
Forearms	0☐	1■	2☐	3☐	0☐	1■	2☐	3☐
Upper Arms	0☐	1■	2☐	3☐	0☐	1■	2☐	3☐
Face			0☐	1☐	2■	3☐		
Anterior Chest			0☐	1■	2☐	3☐		
Abdomen			0☐	1■	2☐	3☐		
Thighs Text Text	0☐	1■	2☐	3☐	0☐	1■	2☐	3☐
Legs	0☐	1■	2☐	3☐	0☐	1■	2☐	3☐
Feet	0☐	1☐	2■	3☐	0☐	1☐	2■	3☐
Column Totals								
Total:	24							

Key: *0 – No Thickening* *1 – Mild Thickening* *2 – Moderate Thickening* *3 – Severe Thickening*

*A score of 24 indicates moderate to severe skin involvement in systemic sclerosis

Figure 3: Rodnan score. From Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, *et al.* Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2017;2:11-8.[6]

be used for both conditions are methotrexate, azathioprine, and cyclophosphamide.[2]

The main complication of skin fibrosis is the development of digital ulcerations. In the diffuse form, however, fibrosis occurs early and together with inflammation, joint pain and shows a rapid spreading to almost all parts of the integument.

Ominous signs such as hypertension, nephritis, systemic vasculitis, and central nervous system disease should be monitored, as well as regular, frequent flares and clinical assessment (physical examination, symptoms monitoring, laboratory tests to assess disease activity organ damage).

The most common cause of death in SSc is pulmonary hypertension. It is vital to monitor and evaluate lung capacity and potential for pulmonary fibrosis because it significantly worsens the outlook. Some patients may also develop scleroderma renal crisis and can have permanent renal damage, although the use of some medications like angiotensin-converting enzyme inhibitors may help in the recovery of renal functions in most cases.

In general, treatment is individualized based on the specific connective tissue diseases involved and the patient's symptoms. Multidisciplinary care is crucial for timely management and to adjust treatment as needed, given the potential for life-threatening complications involving cutaneous and internal organs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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