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Case Report

Clinical features and evaluation of systemic sclerosis: A dermatology-based case series

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Abstract Systemic sclerosis (SSc) is a rare, complex immune mediated connective tissue disease characterized by progressive skin fibrosis and other clinically heterogenous features. Timely referral and early diagnosis of organ manifestations are essential to allow intervention before organ damage occurs. Three patients (2 females and 1 male), aged 23, 34, and 48 years old were identified with a diagnosis of SSc. Duration of the disease was 3 to 5 years with absence of SSc positive family history. Each patient had a clinically SSc with characteristic cutaneous findings according to the ACR/ EULAR (American College of Rheumatology/European League against Rheumatism) 2013 diagnostic criteria. All patients had skin thickening of the fingers, abnormal nail-fold capillaroscopy, and Raynaud's phenomenon. One patient had a non-trauma related digital tip ulcer and another patient presented with facial telangiectasia. SSc related autoantibody (anti-topoisomerase I) was detected in 2 patients while the remaining 1 patient was positive for anti RNP/Sm. Non-SSc related Anti-Ro/ SSA autoantibodies were also detected in 2 patients. Histopathology examination of each patient were consistent with SSc. Patients were multi-specialties managed due to the multifaceted clinical manifestations of SSc. A wide spectrum of clinical phenotypes and autoantibodies of SSc may be observed. The skin provides a window to systemic progression in SSc, allowing dermatologists to contribute to early diagnosis, treatment initiation, effective disease monitoring, and improved patient outcomes.

Key words
Connective tissue disease; Raynaud's phenomenon; Scleroderma.

Introduction

Scleroderma, also known as systemic sclerosis (SSc) is a chronic heterogenous autoimmune connective tissue disease with no recognized cause that results in excessive collagen deposition in the skin and internal organs as well as widespread microvascular damage.[1] Systemic sclerosis is a rare disease worldwide, as well as in the Asian population.[2]

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The most common symptoms of systemic sclerosis were skin fibrosis. The cause is unknown. There are a variety of clinical signs and symptoms. Systemic sclerosis normally progresses over time that frequently involve multiple organs. Endothelial cell damage is thought to be the main cause of SSc pathogenesis which then followed by abnormal vascular and immunological responses.[1]

According to previous studies, racial characteristics in SSc have a substantial impact on the disease's epidemiology, clinical symptoms, antibody profile, mortality, and genetic factors. Asian patients have a unique genetic predisposition to SSc where initiation of the disease occurs at a younger age. Diffuse skin involvement is more common among Asians.

Unusual autoantibody profiles usually present and the clinical symptoms are more severe.[3] Unfortunately, the number and descriptive study of SSc among Asians, particularly South East Asians are rarely being reported.[4]

Interpersonal diversity is a prominent aspect of SSc. Clinical variations has been seen in clinical symptoms, autoantibody profiles, period of disease progression, therapeutic response, and survival. Patients are divided into two groups: those with diffuse cutaneous systemic sclerosis (dCSSc) and those with limited cutaneous systemic sclerosis (dCSSc). Autoantibodies are particularly useful in the diagnosis and prognosis of SSc. Diffuse cutaneous SSc is more frequently related with topoisomerase I- or RNA polymerase III-specific antibodies, while lcSSc is frequently related with centromere-specific antibodies. However, not all SSc patients clearly fit into one of these two disease sub-sets and some can evolve over time.[3]

Specific patients' medical history analysis alone is not the best way to comprehend the complexity of SSc. There are experiences need to be shared and new understandings to be learned among the variety of complex and therapeutically hard situations portrayed. Herein we report this case series of systemic sclerosis in 3 patients whom seen in a Dermatology and Venereology Department of a tertiary hospital in West Sumatera, Indonesia from the period of January 2022 to December 2022.

Case reports

Case 1 A 34-year-old woman with chief complain of whitish patches associated with skin stiffness on the neck that worsen in the past 4 years. Initially, patient noted the appearance of painless and non-pruritic whitish patches on the neck then the lesions evolved into whitish patches with coexistence of hyperpigmentation to involve the upper back, upper chest, face and scalp area associated with progressive skin tightness, hair thinning, occasional fatigue and weakness, palpitation and shortness of breath.

Patient had a history of blanching and bluish discoloration of the fingertips when exposed to cold and psychological stress. Patient denied of having any history of dysphagia, sun-induced skin rashes on both cheeks, muscle weakness, rashes on the trunk and extremities, arthralgia, diarrhea, dyspepsia, urinary disturbance, acral edema, nor increased blood pressure. Family medical history was unremarkable.

General physical examinations were non-contributory with normal vital signs. Dermatologic examinations showed scattered milky white depigmentation coexistence with peri-follicular hyperpigmentation with a "salt and pepper" configuration and skin hardening involving the forehead, neck, chest, upper back, and dorsum of both hands. Examination on the extremities showed symmetrical stiffness of the skin involving both hands with missing of skin furrows over the dorsum of distal fingers (puffy fingers), cold on palpation and digital tip ulcer on the 4th digit of right hand **(Figure 1)**. Total score of modified Rodnan Skin Score (mRSS) of 17 different anatomical areas in this patient was 19.

Dermoscopy of the dyspigmented lesions revealed irregularly shaped white homogenous areas with perifollicular pigmentation. Nail fold capillaroscopy showed an active pattern of scleroderma with the features of large capillaries, capillary hemorrhage, and capillary dropout (evident loss of capillaries) **(Figure 2)**.

Anti-nuclear antibody (ANA) profile showed positive (+2) for anti-RNP (ribonucleoprotein)/ Sm (Smith) and borderline (+) for recombinant (Ro)-52. Skin punch biopsy of the dyspigmented

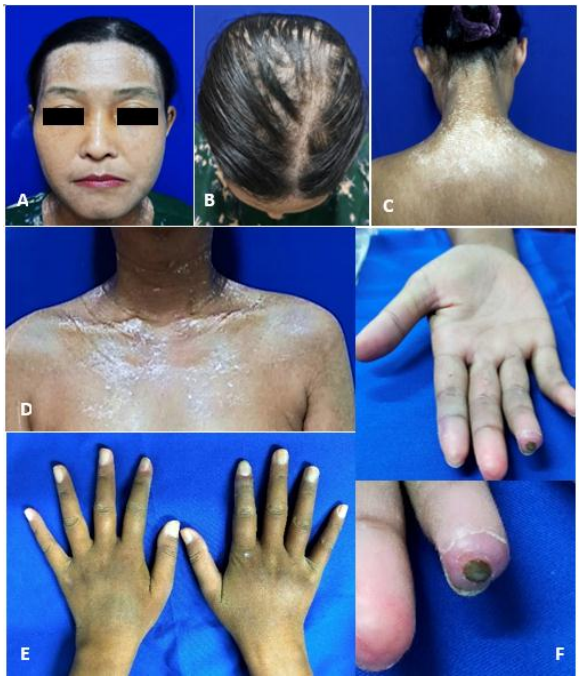

Figure 1 Scattered vitiligo-like depigmentation coexistence with perifollicular hyper-pigmentation with a salt and pepper-like configuration and skin hardening involving the (A) forehead, cheeks, (B) scalp, (C & D) neck, chest, upper back, and (E) dorsum of both hands and symmetrical hardening of the skin involving both hands with loss of skin creases over dorsum of distal hands fingers (puffy fingers). Examination on the extremities showed (F) digital tip ulcer on the 4th finger of the right hand.

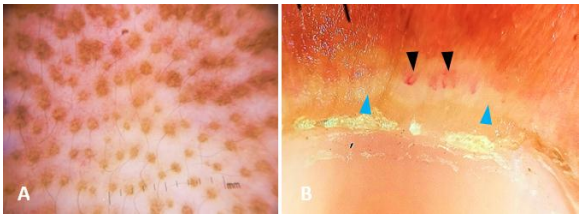

Figure 2 (A) Dermoscopy of the dyspigmented lesions revealed irregularly shaped white homogenous areas with perifollicular pigment (B) Nail fold capillaroscopy: Late scleroderma pattern: Avascular areas (blue arrowhead) with dilated capillaries (black arrowhead). (Heine Delta One. Polarized view).

lesion on the back revealed densely thickened collagen bundles and entrapped atrophic adnexal structures **(Figure 3)**.

Diagnosis of SSc was established based on the history, clinical manifestations, and

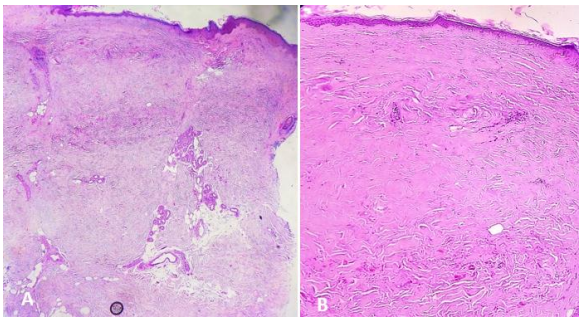

Figure 3 Histopathology showed (A) atrophy of the epidermis. The dermis revealed densely thickened collagen bundles and entrapped atrophic adnexal structures in the deep dermis (B) Thickened collagen bundles in the dermis more prominent highlighted with higher magnification (H&E. 100x).

autoantibodies detection. She was co-managed with rheumatology department and was treated with oral methylprednisolone 16 mg per day, oral hydroxychloroquine 200 mg once daily, and topical moisturizer containing 10% urea daily. Patient was also advised to consult with pulmonology, gastro-enterology, renal, and cardiology department regularly.

Case 2 A 48-year-old male seen at the Dermatology and Venereology Clinic with chief complaint of progressive skin tightening and dyspigmentation on the scalp, neck, shoulder and upper back associated with fatigue in the past 5 years. Patient was also developed occasional fatigue and weakness which were not related with exercise or psychological stress. Patient had a history of blanching and bluish discoloration of the fingertips due to cold exposure and psychological stress. He also had non-productive cough and occasional shortness of breath. History of stiffness in both hands accompanied by difficulty in grasping both of hands and digital ulcer were denied.

Patient denied of having any history of dysphagia, sun-induced skin rashes on both cheeks, muscle weakness, rashes on the trunk and extremities, arthralgia, diarrhea, dyspepsia, urinary disturbance, nor acral edema. There was no history of previously diagnosed auto-immune

disorder, renal disease, nor diabetes. History of family member SSc was denied.

General physical examinations were normal, blood pressure was 110/70 mmHg. Dermatologic examinations showed scattered vitiligo-like depigmentation coexistence with a salt and pepper-like configuration and skin hardening including the scalp, face, neck, chest, upper back, and shoulders. Examination on the extremities showed symmetrical loss of skin creases over dorsum of distal hands fingers (puffy fingers) and cold on palpation **(Figure 4)**. Total Score of mRSS was 18.

Dermoscopic picture of the lesions were obtained from the dyspigmented patches revealed irregularly shaped white homogenous areas with the presence of peri-follicular pigment. Nail fold capillaroscopy showed giant capillaries, capillary hemorrhage, and capillary dropout **(Figure 5)** which encompass the active SSc pattern.

Anti-nuclear antibody profile showed positive (+3) for Scl-70. Histopathhologic examination of the dyspigmented lesion on the back revealed densely thickened collagen bundles with peri-adnexal mild inflammatory cells infiltration **(Figure 6)**. Lung Computed Tomography (CT) scan revealed the absence of interstitial lung disease (ILD).

Patient was diagnosed with systemic sclerosis. He was treated with oral methylprednisolone 4 mg daily, methotrexate 12.5 mg/week, folic acid 5 mg/week once daily, nifedipine 5 mg twice daily, cilostazole 100 mg once daily, and topical moisturizer containing 10% urea daily. He was co-managed with rheumatology, pulmonology, gastro-enterology, renal, and cardiology department.

Case 3 A 23-year-old female sought consult with skin tightening of the fingers in the last 3 years. She noted appearance of whitish asymptomatic patches on her scalp. The disease started with progressive skin tightening of her fingers associated with painful sensation due to cold exposure. Digital skin tightening was

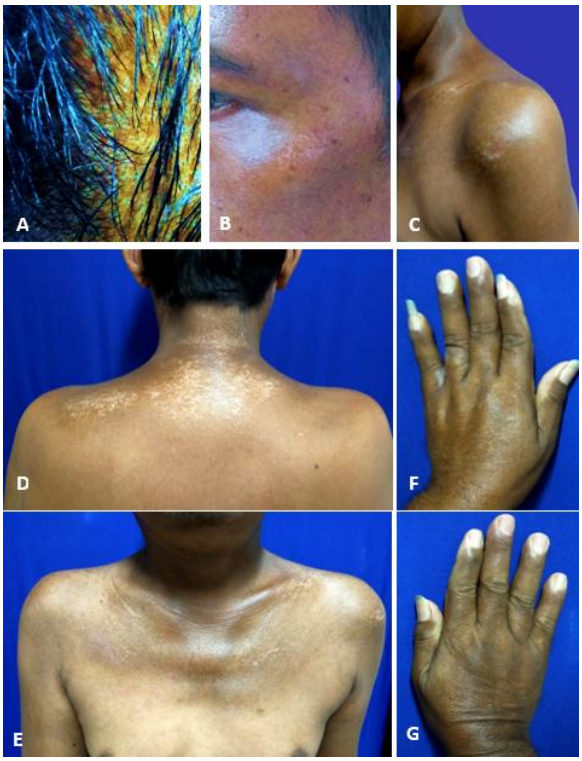

Figure 4 Scattered vitiligo-like depigmentation coexistence with perifollicular hyperpigmentation with a salt and pepper-like configuration and skin hardening involving the (A) scalp, (B) face, (C) shoulder, (D & E) neck, upper chest, upper back. Examination on the extremities showed (F & G) puffy fingers.

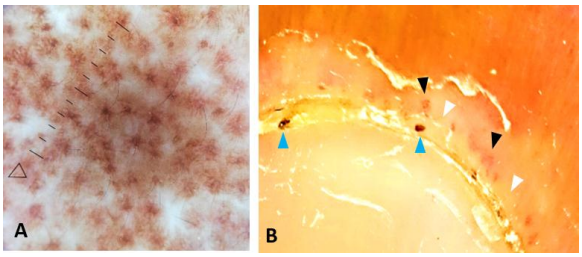

Figure 5 (A) Dermoscopy of the dyspigmented lesions revealed irregularly shaped white homogenous areas with perifollicular pigment, (B) Nail fold capillaroscopy: Active scleroderma pattern: giant capillaries (black arrowhead), capillary hemorrhage (blue arrowhead), and capillary dropout (white arrowhead) (Heine Delta One. Polarized view).

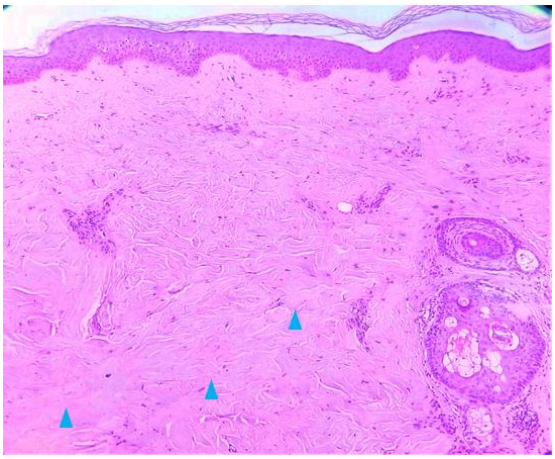

Figure 6 Histopathology examination of the dyspigmented lesion densely thickened dermal collagen bundles with peri-adnexal mild inflammatory cells infiltration (blue arrowhead). (H&E 100x).

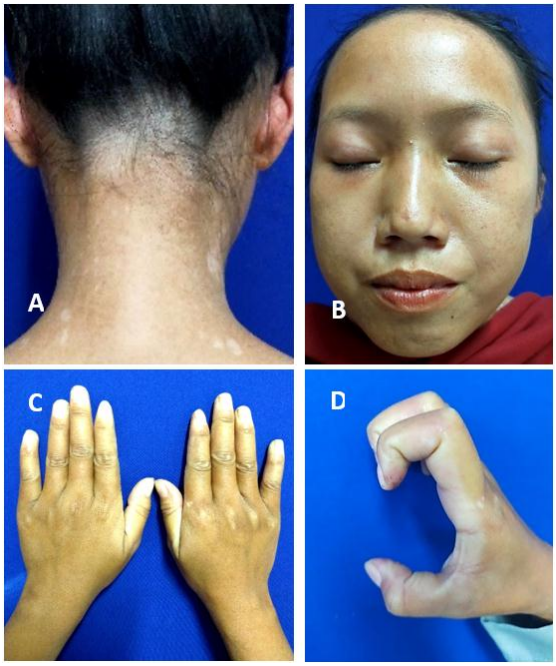

Figure 7 (A) Dermatologic examinations showed scattered whitish macules coexistence with interspersed perifollicular hyperpigmentation and skin hardening involving the scalp. (B) Skin tightening with telangiectasia on the malar area were also seen. Examination on the extremities showed (C) sclerodactyly, puffy fingers and cold on palpation with (D) limited phalangeal range of motion.

worsen with limitation in range of movement of her fingers. She also experienced skin tightening on her face, dysphagia, dyspepsia, occasional episodes of palpitation, shortness of breath, and fatigue with unknown triggering factor. There was no history of previously diagnosed auto-immune disorder, renal disease nor diabetes. History of family member with SSc was absent.

Dermatologic examinations showed scattered whitish macules coexistence with interspersed perifollicular hyperpigmentation and skin hardening involving the scalp and neck. Skin tightening with telangiectasia on the malar area were also seen. Examination on the extremities showed sclerodactyly and cold on palpation **(Figure 7)**. History of digital ulcer was absent. Total Score of mRSS was 11.

Anti-nuclear antibody (ANA) profile showed positive (+3) for Scl-70, SS-A, and Ro-52. Histopathology of the tightened skin on the finger revealed the "hallmark" sign of thickened dermal fibro-collagen bundle with infiltration of peri-adnexal mild inflammatory cells **(Figure 9)**. Chest CT scan showed the absence of pulmonary involvement.

According to the clinical and ancillary examinations, she was diagnosed with SSc. Oral methylprednisolone 4 mg daily, oral methotrexate 12.5 mg/week, oral folic acid

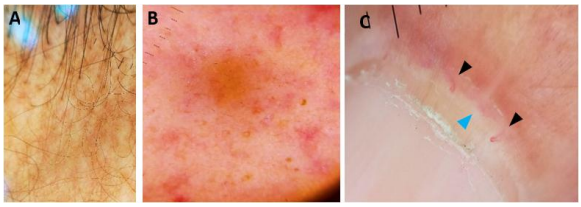

Figure 8 (A) Dermoscopy of the dyspigmented lesions revealed irregularly shaped white homogenous areas with perifollicular pigment (B) Dermoscopy of the malar area showed "spot and matted" pattern telangiectasia. (C) Nail fold capillaroscopy: Nail fold capillaroscopy: Late scleroderma pattern: Avascular areas (blue arrowhead) with dilated capillaries (black arrowhead). (Heine Delta One. Polarized view).

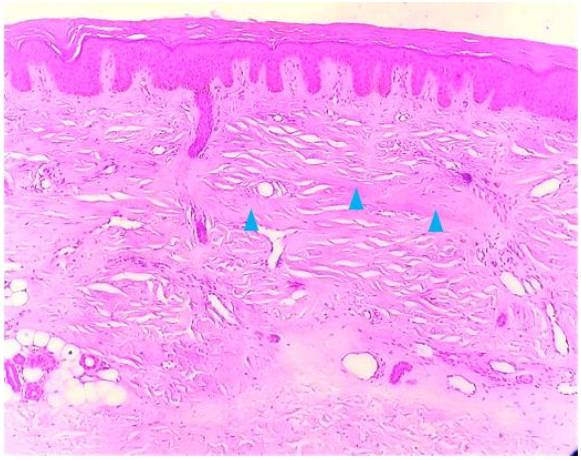

Figure 9 Histopathology examination of the hardened lesion revealed the squamous epithelial cells of the epidermis. The dermis showed densely thickened fibro-collagen bundles with peri-adnexal mild inflammatory cells infiltration (blue arrowhead). (H&E 100x).

5 mg/week once daily, oral cilostazole 100 mg once daily, oral lansoprazole 30 mg once daily, and topical moisturizer containing 10% urea daily were prescribed. Patient was also managed in collaboration with rheumatology, pulmonology, gastro-enterology, renal, and cardiology department.

Discussion

An immune-mediated condition known as systemic sclerosis poses a significant clinical challenge for both patients and physicians. The heterogeneity of the disease's symptoms and history makes SSc diagnosis challenging.[5] The varied nature of SSc is evidently influenced by racial and geographic differences.[3]

The annual incidence of SSc is estimated to be 1.4 per 100,000 per person-years, whereas the prevalence is 17.6 cases per 100,000 persons.[4] Female are more likely than male to develop SSc with a ratio ranging from 3:1 to 14:1.[2] A positive family history increases the relative risk of SSc by 12-fold compared to the population without genetic predisposition.[5] In this three cases, female patient was more dominant than male patients (2 female and 1 male). There was no family history of SSc among patients in this report.

Asian SSc patients have younger onset and diagnostic ages than Caucasian SSc patients.[6] According to the European Scleroderma Trials and Research (EUSTAR) cohort, Asian patients' mean age at SSc diagnosis was 38.1 years, younger than that of Caucasian patients (44.2 years).[7] Other SSc studies conducted in China, Singapore, Japan, Korea, India and Iran revealed that Asian SSc patients were 10 to 20 years younger compared with the Caucasians.[3] Our patient's disease onset were 34 years, 48 years and 23 years for case I, II, and II respectively. Genetic variable factors may modulate immune responses and cause autoimmune disease including SSc age of onset in our patients.

Early microvascular damage, mononuclear-cell infiltrates, and slowly advancing fibrosis are characteristic features of the tissue lesions at different phases of SSc. Later stage of SSc is characterized by atrophy, cell loss, and extremely tight-packed collagen bundle in the dermis. The clinical prognosis is determined by the pathological alterations in the heart, lungs, gastrointestinal tract, kidneys, and skin. However, skin fibrosis is the distinctive feature of SSc. The severity of problems affecting the visceral organs is typically reflected in the extent of skin involvement and its rate of advancement.[1] Early cutaneous manifestation or rapid progressive skin involvement in SSc is associated with the high prevalence and severity of internal organ involvement.[8]

More than 90% of SSc patients experience Raynaud's phenomenon. The hands are typically affected, while the feet are less frequently. The typical trigger is exposure to cold, although symptoms can also be caused by emotional stress. Patients with SSc may have puffy hands

which manifested as swollen fingers and hands for extended periods of time at the beginning of the condition, especially in the diffuse form. Sclerotic alterations eventually result in cutaneous contractures, sclerodactyly, perioral plication, microstomia, and stiffness that resembles a mask. They may also be accompanied by other symptoms including hair loss, decreased sweating, hyper- or depigmentation, or intense itching. Internal organ involvement may worsen as the disease progresses, whereas truncal and proximal extremities skin fibrosis will diminish.[5]

Patient's self-report or physician's report of Raynaud's phenomenon is valid to be recorded as one of the diagnostic approach. A condition with at least a 2-phase digital color change consisting of pallor, cyanosis, and/or hyperemia induced by cold exposure or emotion (usually one phase is pallor) is a sign of positive Raynaud's phenomenon.[9] All patients in this report were presented with a history of Raynaud's phenomenon.

Cutaneeous calcinosis, fatigue, musculoskeletal pain, and other chronic pain syndromes are non-fatal symptoms of scleroderma which also associated with the disease course. Deposits of subcutaneous calcium carbonate deposition found on the acral regions may present in all SSc sub-types. They could result in superficial erosions and give the patient excruciating discomfort.[5] Physical and radiologic examination of the patients in this report did not show any abnormalities of the musculoskeletal system.

The 2013 ACR/EULAR criteria updated the recent diagnostic criteria in SSc. The new insights on the importance of vascular abnormalities and nailfold capillaroscopy in addition to the previous focus on the presence of fibrosis improve the diagnostic accuracy of SSc. A total score of the 2013 ACR/EULAR criteria ≥9 denotes systemic sclerosis.[4,9] All patients in this case series were positive of SSc according to that criteria **(Table 1)**.

Patients with SSc often have between 15 and 25 percent active digital ulcerations and 35 percent either currently have them or had in the past.

Table 1 American College of Rheumatology/European League against Rheumatism 2013 criteria for classification of systemic sclerosis.

Item	*Subitems*	*Score*	*Case I*	*Case II*	*Case III*
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints	-	9	-	-	-
Skin thickening of the fingers	Puffy fingers	2	2	2	Yes
	Sclerodactyly (distal to Metacarpo Phalangeal joints but proximal to Proximal Interphalanx joint)	4	-	-	4
Fingertip lesions	Digital tip ulcers	2	2	-	-
	Finger tip pitting scars	3	-	-	-
Telangiectasia	-	2	-	-	2
Abnormal nail fold capillaries	-	2	2	2	2
Pulmonary changes	Pulmonary arterial hypertension	2	-	-	-
	Interstitial lung disease	2	-	-	-
Raynaud's phenomenon		3	3	3	3
SSc-related autoantibodies in serum (any of the listed antibodies)	Anti-centromere Anti-topoisomerase-1 (anti-scl 70) Anti-RNA polymerase III	3	-	3	3
Total			9	10	14

Nonetheless, this proportion varies greatly between research and facilities. While ulcers on the extensor surfaces of the proximal and distal interphalangeal joints are typically caused by a combination of inadequate perfusion, stretched fibrotic skin, and trauma; ulcers on the fingertip are thought to be entirely caused by ischemia.[5] Patient in case I developed digital tip ulcer. Telangiectasias are the ordinary skin manifestations of microvascular changes in SSc. Telangiectasias in SSc are well demarcated and round-shaped and/or are large mat-like pattern, usually found on face, hands, lips, oral mucosa.[5,8,9] As a result of normal circulation impairment in the affected tissues, the process causing the development of telangiectasia may be as a result of an erroneous attempt to increase blood perfusion to hypoxic tissues. Telangiectasias may therefore indicate persistent vascular damage and inadequate vascular healing, both of which are considered to affect several important organs in SSc.[10]

Nail fold capillaroscopy is a practical and noninvasive technique that can assist the diagnosis of progressive connective tissue disorder. It also aids in reflecting the severity and stage of microvascular damage. In connective tissue disorders, systemic vasculopathy affects the capillary architecture of the nail fold, which causes bleeding and loss of capillaries. Giant capillaries serve as an example of an aberrant angiogenic response to peripheral ischemia. Capillary hemorrhages are an example of Raynaud's phenomenon, and numerous ones are more indicative of SSc.[11] However, nail fold capillaroscopy unable to distinguish SSc from other connective tissue diseases which have capillaroscopy feature of "scleroderma-type" changes, such as: dermatomyositis, other (mixed) connective tissue diseases.[12,13]

Scleroderma pattern of capillaroscopy defined as the presence of two or more abnormalities such as dilated capillaries, avascular pattern (drop out), giant capillaries, and capillary hemorrhage.[12,14] The patterns depicted in SSc are classified into: 1) Early scleroderma; 2) Active scleroderma; and 3). Late or evolved scleroderma.[13]

Patients in this report presented with scleroderma spectrum of nail fold capillaroscopy. Vascular anomalies in the nail folds reflect the pathophysiological process that underlies this disease: chronic hypoxia modifies capillaries and promotes neo-angiogenesis under the control of various growth factors (including VEGF and PDGF) in a profibrotic environment. This dynamic process begins with the dilatation of the labile and fragile capillaries, which cause microhemorrhages. These initial changes corelate with the early SSc capillaroscopy pattern. As this process advances, the capillary abnormalities will occur throughout the nail bed, configuring and active pattern; later, the affected capillaries disappear, resulting in avascular areas, reflecting the late pattern.[11]

The presence of ANA, which is found in more than 90% of SSc patients, is one distinguishing feature of the immunological abnormalities in this disease. The most common ANA discovered in people with SSc are anti-centromere antibodies, anti-DNA topoisomerase I antibodies (Scl 70), and anti-RNA polymerase III antibodies. Other anti-nuclear antibodies linked to SSc target ribonucleoprotein, Th/To, and eukaryotic initiation factor 2B.[15]

Systemic sclerosis patients whom positive anti-Scl-70 autoantibody tend to have ILD. Fifteen to twenty percent of SSc patients have anti-Scl-70 antibodies. Asian individuals were more likely (30-80%) to have anti-Scl-70 autoantibodies than anti-centromere autoantibodies.[7] This is consistent with detected autoantibody in this report where patients in case II and III were

positive for Scl-70. However, none of them were HRCT (High-resolution computed tomography) positive for ILD. Periodic annual follow-up and lung examination is strongly advised for these patients.

Systemic sclerosis overlap syndrome relates to ribonucleoprotein (RNP) antibodies. Anti-human upstream binding factor and anti-Ro52 antibodies are occasionally seen in sera from systemic sclerosis patients, despite not specific to the disease.[15] According to a previous study of Asian SSc patients in the United States and Canada, RNP antibodies were more common among Asians than among Caucasians (32.1% and 11.9%, respectively).[6] Previous cohort studies among Asians in Asian region showed antibody similarity with high anti-U1-RNP prevalence (24–33%).[16] Patient in case I was positive for RNP antibody. Anti-U1-RNP is often found to be related with mixed connective tissue disease (MCTD) or overlap syndromes. However, patient in case I did not qualify for the diagnosis of MCTD or overlap syndrome. Regular follow-up and evaluation were planned for this patient to observe and prevent development of the possible disease evolution into MCTD or overlap syndromes.

The positivity rate of anti-Ro/SSA in SSc varies from 3% to 37%.[17,18] Ro antigens consist of two distinct proteins, SSA/Ro60 and SSA/Ro52, which are present in two different cell compartments. Anti-SSA/Ro antibodies have been tested in patients with autoinmune diseases, including SSc. Patient in case III was positive for SSA/Ro60 autoantibody. Sánchez-Montalvá A (2014) reported that anti-SSA/Ro52 antibodies are frequently identified in SSc patients. In that study, no clinical symptoms, including inflammatory myopathy were linked to anti-SSA/Ro antibodies.[18] It is probably that the etiopathogenetic pathways marked by these antibodies have common components, including common genetic predispositions. Other report by Antonioli C, *et al.* (2002) showed that anti-Ro+ SSc patients are more prone to acquire earlier lung involvement.[17] Hence close monitoring for our patients is advised.

The most noticeable clinical symptom of the disease in people with SSc is an aberrant accumulation of extracellular matrix components in the skin. Early skin lesions are distinguished by the presence of inflammatory cell infiltrates that are primarily made up of activated T cells surround the thickened collagen bundles that run parallel to the skin's surface within the reticular dermis. Advance stages of SSc are characterized by fewer inflammatory cells and excessive accumulation of densely packed eosinophilic collagen fibers leading to increased skin thickness with absent of adnexal tissue.[19] The later stage of SSc pathologic features were present in our cases' histopathologic findings.

The chronic and erratic nature of the disease's course necessitate at least yearly patient follow-up. The treatment of classic organ involvement should not be the only focus of multidisciplinary therapy for SSc patients. The importance of addressing the patient's quality of life should become more widely recognized and endeavored.

Conclusion

Systemic sclerosis is a complex multi-system connective tissue disease. The diagnosis of SSc is established according to clinical manifestations, autoantibody profiles, and additional specific investigations addressing specific organ involvement. It is important for dermatologists, as part of the multidisciplinary care team, have a thorough understanding of individual organ manifestations, the complex course of the disease and their associated

treatment. Timely diagnosis, work-up, and initiation of disease-modifying treatments is vital in the management of SSc. Prompt screening, treatment, and monitoring for progression of organ-based manifestations in SSc is crucial to reduce morbidity and mortality.

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