

## Letter to Editor

## Pre-Scleroderma State

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## Abstract

Scleroderma is divided into localized and systemic. Localized Scleroderma is a cutaneous disease with only sclerosis of one or more skin area without Raynaud's phenomenon (RP) and visceral involvement, but systemic Scleroderma [or systemic sclerosis] is a chronic autoimmune multisystem disorder with overproduction of collagen fibers; presented as a combination of thickened/sclerotic skin involvement and visceral organ fibrosis along with Raynaud's phenomenon. The pathogenesis of this disease is unknown but upon a genetic background, environmental trigger factors can initiate the pathophysiology of it. Its pathophysiology has three axes: Vascular events including Raynaud's phenomenon and endothelial injury, immunological events and activated fibrogenic fibroblast. When complex interplay between basal vasculopathy and autoimmunity affects fibrogenic fibroblasts, it initiates and amplifies the fibrotic process and in this stage the disorder will be irreversible/progressive and it is not curable or even, treatable. So, we need to diagnose the state before the start of fibrosis of skin and viscera. This state can be called as pre-scleroderma state. In this letter, the corresponding author wants to deliver a diagnostic criteria for pre-scleroderma state. If in this step, the problems can be detected, it may be prevented, but after establishment of scleroderma, it cannot be curable or treatable.

## INTRODUCTION

Scleroderma is divided into localized and systemic. Localized Scleroderma is a cutaneous disease with only sclerosis of one or more skin area without Raynaud's phenomenon and visceral involvement [1]. But, systemic Scleroderma [or systemic sclerosis] is a chronic autoimmune multisystem disorder with overproduction of collagen fibers; presented as a combination of thickened/sclerotic skin involvement and visceral organ fibrosis along with Raynaud's phenomenon [2,3].

The pathogenesis of this disease is unknown but upon a genetic background, environmental trigger factors can initiate the pathophysiology of it. Its pathophysiology has three axes [4].

- Vascular events including Raynaud's phenomenon and endothelial injury
- Immunological events
- Activated fibrogenic fibroblast

When complex interplay between basal vasculopathy and autoimmunity affects fibrogenic fibroblasts, it initiates and amplifies the fibrotic process and in this stage the disorder will be irreversible/progressive and it is not curable or even, treatable [5].

So, we need to diagnose the state before the start of fibrosis of skin and viscera.

This state can be called as pre-scleroderma state. It must be differentiated from early scleroderma and systemic sclerosis sine scleroderma.

Early scleroderma is the initial stage of scleroderma in which puffiness of hands/feet with or without facial puffiness can be seen. After that scleroderma follows two courses [3]:

- Limited cutaneous scleroderma [LcSSc]
- Diffuse cutaneous scleroderma [dcSSc]

In limited type, the skin sclerosis is restricted to distal portion of extremities and face, so it is famous as acro-facial scleroderma. But in diffuse type, the skin sclerosis will be propagated toward proximal portion of extremities, scalp and especially trunk. This type is called trunkal scleroderma too. The sclerosis of hand proximal to MCPs is the hallmark of disease. This along with sclerodactyly and pitting ulcer are the most important features in hands [6,7]. Facial features of scleroderma are including:

- Shiny, masklike/expressionless face
- Decreased skin fold
- Microstomia [fish mouth]
- Perioral radial furrowing
- "Beak-like" nose
- Omega sign

**Table A:** Iran Diagnostic criteria of Pre-Scleroderma state <sup>a,b</sup>.

<b>Secondary Raynaud's phenomenon<sup>c</sup></b>	Up to 2 points
Age onset > 30 years	1 point
Male gender	1 point
Painful RP	1 point
RP along with digital ulceration and gangrene	2 points
Asymmetric RP	2 points
<b>Nail fold capillary abnormalities<sup>c</sup></b>	Up to 2 points
Enlarged capillary loops	1 point
Distorted capillary loops	1 point
<b>Laboratory findings</b>	Up to 2 points
Abnormal CBC and/or elevated ESR <sup>c</sup>	1 point
Positive ANA <sup>c</sup>	1 point
Positive ACA and/or Scl-70 and/or Anti-RNA polymerase III	2 points

RP: Raynaud's phenomenon; ANA: Anti-nuclear antibody; ACA: Anti-centromere antibody; Scl-70: Anti-topoisomerase I; CBC: cell blood count; ESR: Erythrocyte sedimentation rate.

- Entry criteria: No cutaneous/visceral involvement compatible with scleroderma.
- With at least 4 points out of 6 the definite diagnosis of pre-scleroderma can be established. With 2 to 3 points probable to highly suggestive pre-scleroderma is a proper diagnosis.
- No other etiologies upon history and physical examination.

- Mat like telangiectasia

In both limited and diffuse scleroderma, visceral involvement can be seen but in diffuse type this involvement is widespread and rapidly progressive. The most important visceral involvement of scleroderma are including [8,9]:

- Gastrointestinal: Dysphagia/ Gastro-esophageal reflux disorder [GERD]/ Intermittent diarrhea-constipation
- Lungs: Interstitial Lung Disease [ILD]/ Pulmonary artery hypertension [PAH]
- Renal: Sclerodermal renal crisis [SRC]
- Heart: Myocardial fibrosis/ Conduction defects and so on.

Other manifestations are including musculoskeletal involvement, endocrine/exocrine gland involvement and so on.

The scleroderma with visceral fibrosis without skin sclerosis is systemic sclerosis sine scleroderma [10]. Raynaud's phenomenon [RP] is a sequential color changes in the digits due to arterial vasoconstriction precipitated by cold, stress and vibration. Triphasic color changes are including white, blue and red. For definite Raynaud's phenomenon, repeated episodes of biphasic color changes after exposing to cold is enough [11].

Up to 5% of general population are involved with primary Raynaud's phenomenon that is not pathologic but the pathologic Raynaud's phenomenon is secondary to etiologic disorders or taking causal drugs [12].

Systemic scleroderma, Systemic Lupus Erythematosus [SLE], Dermatomyositis and vasculitides are the most important Rheumatic disease accompanied by RP [13].

Clinical clues to suggest secondary RP are including [11,14]:

- Late age of onset [>30 years]
- Male gender
- Painful RP
- RP with digital ulceration and gangrene
- Asymmetric attacks
- RP associated with other signs or symptoms
- Abnormal CBC, elevated ESR and positive autoantibodies

Abnormal nail fold capillary microscopy can be seen in many disorders especially systemic sclerosis, SLE, Dermatomyositis, Behcet's disease and so on.

The combination of enlarged capillary loops and loss of capillaries is more suggestive for systemic scleroderma [15]. Many different autoantibodies can be seen in systemic scleroderma including ANA, Anti-centromere antibody [ACA], Anti-topoisomerase I [Scl-70], Anti RNA polymerase III and so on. Among them ANA is the most sensitive autoantibody. ACA is sensitive in 70-80% of limited scleroderma and it is specific for this type of scleroderma [16]. Scl-70 is sensitive in 30% of diffuse scleroderma and it is specific for this type of scleroderma.

By this letter, corresponding author want to deliver a diagnostic criteria for pre-scleroderma state. If in this step, the problem can be detected, it may be prevented, but after establishment of scleroderma, it cannot be curable or treatable. Along with it an accessory criteria for detection of systemic sclerosis sine scleroderma will be delivered too. Finally the corresponding author would like to ask the members of ACR, EULAR, APLAR and all of the Rheumatologists in the world to evaluate this criteria. I must inform you that because of funding problem, we cannot evaluate it.

**Table B:** Visceral criteria for systemic Sclerosis sine Scleroderma <sup>a</sup>.

Gastrointestinal involvement
<ul style="list-style-type: none"> <li>Dysphagia and/or GERD</li> <li>Watermelon stomach and/or Gastric antral venous ectasia (GAVE)</li> </ul>
Lung disease
<ul style="list-style-type: none"> <li>Interstitial Lung Disease and/or pulmonary artery hypertension (PAH)</li> </ul>
Renal involvement
<ul style="list-style-type: none"> <li>Sclerodermal renal crisis (SRC) <sup>b</sup></li> </ul>
Heart lesion
<ul style="list-style-type: none"> <li>Myocardial fibrosis and/or conduction defect</li> </ul>

- In the case of definite pre-scleroderma, with at least one of visceral criteria, systemic sclerosis sine scleroderma can be established. In probable to highly suggestive pre-scleroderma state (Table A), with at least two visceral criteria, systemic sclerosis sine scleroderma can be confirmed too (Table B).
- SRC: means Acute Renal Failure along with 3 to 4 of below items:
  - Normal urinalysis
  - Abrupt onset of marked hypertension
  - Pericarditis and/or heart failure
  - Microangiopathic hemolytic anemia

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