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Systemic Sclerosis: An Oral Pathologist Perspectives

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Abstract: Systemic sclerosis (SSc) also known as scleroderma is an uncommon, complex, multisystem disorder of connective tissue. It presents with heterogenous clinical manifestations and is characterized by its chronic and progressive nature, often leading to significant disability and mortality. In the oral cavity, the progressive fibrosis appearances reminiscent of late stages of oral submucous fibrosis. Although like Oral submucous fibrosis, can be distinguished with clinical & immunological findings. This review highlights clinical features, gene involvement, overlapping syndrome, Differential diagnosis and management of SSc.

Keywords: Progressive fibrosis, Autoantibodies, American College of Rheumatology criteria

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INTRODUCTION: Carlo Curzio provided the first description of Systemic Sclerosis (SSc) in 1753. However, the term scleroderma (from the Greek sklerosis meaning “hardening” and derma meaning “skin”) was ascribed only in 1847 by Gintrac.[1] Globally, the prevalence of SSc is estimated to be 17.6 per 100 000 and incidence is estimated to be 1.4 per 100 000. It predominantly affects women with a female to male ratio of 5:1 and manifests between third and the fifth decade of life. [2 3] Despite extensive research, the Etiology of SSc remains indeterminate. However, it is thought by many to be the result of the intricate relationship between immune system dysregulation, environmental exposures, and genetic predisposition. The primary events in the pathogenesis of SSc constitute a triad of microvascular disturbance, immune system activation with autoantibody production and progressive fibrosis of skin and internal organs.[4] Anti-centromere, anti-topoisomerase I (Scl 70), and anti-RNA polymerase III are commonly found to play a critical role in diagnosis. cutaneous involvement, SSc can be clinically classified as localized cutaneous systemic sclerosis (lcSSc),[5] in which affects the skin distal to the elbows and knees and often the face and diffuse cutaneous systemic sclerosis (dcSSc), which involves proximal skin and is more frequently associated with internal organ complications. In rare cases, systemic features present without significant skin involvement, and those are termed as SSc sine scleroderma.[6] Orofacial manifestations are increasingly recognized as critical diagnostic clues. Albilia et al. in their review confirmed that the initial diagnosis of SSc can be made by the dental surgeons highlighting the importance of dental professionals. The orofacial region is among the earliest and most affected sites in SSc, with up to 80% of patients showing signs such as microstomia, xerostomia, limited

mouth opening, telangiectasia, periodontal disease, and resorption of the mandibular angle. [7] Despite considerable advancements, systemic sclerosis continues to pose major diagnostic and therapeutic challenges due to its clinical heterogeneity and unpredictable course. This review aims to provide an updated and structured overview of the current knowledge regarding systemic sclerosis, encompassing its epidemiology, pathogenesis, clinical features, diagnostic workup, and management.

ETIOLOGY: Systemic sclerosis shows familial clustering with low concordance in twins.[9] The specific human leukocyte antigens (HLA), including HLA DRB1*1104, DQA1*0501, and DQB1*0301 are well known to be associated with SSc. Also, some of the Non-HLA loci had been implicated in the etiology which includes PTPN22, NLRP1, STAT4 and IRF5. Certain environmental factors like Cytomegalovirus, Epstein- Barr virus, Parvovirus B19 and silica dust along with occasional exposure to toluene, xylene, trichloroethylene, and polyvinyl chloride also act as triggers.[8]

PATHOGENESIS:

PHENOTYPE:

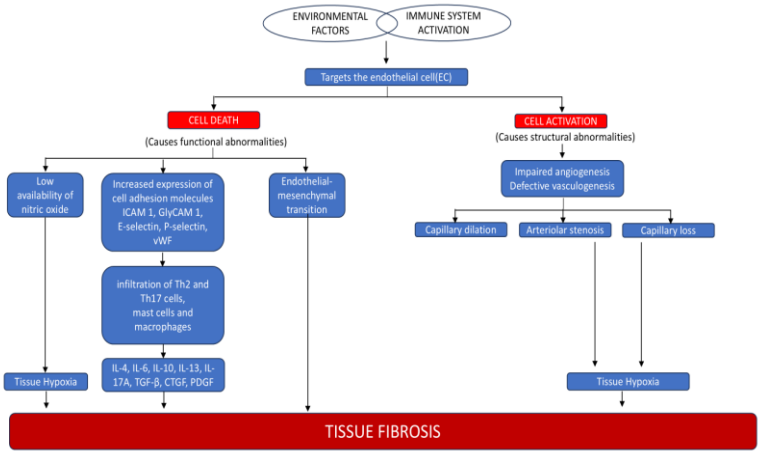
The key events in the pathogenesis of SSc constitutes a triad:

- Microvascular disturbance,
- Immune system activation with autoantibody production and
- Progressive fibrosis.[4]

Microvascular disturbance:

Exposure to certain environmental influences causes aberrant activation of the immune system. Initially, the autoimmune attack is believed to target the endothelial cells, which can undergo two distinct fates; cell death and cell activation. Neovascularization(angiogenesis) and vascular remodelling (vasculogenesis) are impaired in the injured blood vessels, which causes structural changes of the blood vessels [**Flowchart.1**]. Alternatively, endothelial cells are stimulated and express aberrant behavior, leading to fibrosis and inflammation.[9]

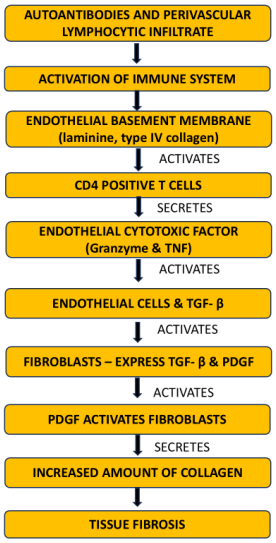
Flowchart 1: Mechanism of Immune system activation



Immune system activation with autoantibody production:

Both innate and humoral immune systems have an essential role in pathogenesis of systemic sclerosis.[8] Inflammatory cells are activated and infiltrate afflicted organs through the interaction of endothelial cells with circulating immune cells.9 The tissue and peripheral blood are primarily composed of activated T lymphocytes and an imbalance is noted in Th1 and Th2 cells where Th2 profile is predominant leading to increased fibrosis. **[Flowchart 2]** The autoantibodies are produced by the activated B cells, which are the diagnostic marker for the disease. [8]

Flowchart 2: Mechanism of fibrosis



Progressive fibrosis:

Autoimmunity caused by vascular injury and inflammation causes tissue fibrosis through mesenchymal cell activation and differentiation leading to uncontrolled fibroblast activation and irreversible extracellular matrix accumulation (ECM).[8] A key growth factor involved in the activation of fibroblasts is TGF-β, a potent inducer of ECM. Lots of α-SMA positive myofibroblasts are present which originate from the resident fibroblasts, bone marrow derived fibrocytes, epithelial-mesenchymal transition, ultimately leading to ECM deposition.[9]

GENOTYPE:

Emerging genomic studies identified several genetic loci associated with distinct SSc subtypes and patterns of organ fibrosis. These genes come under the key immune regulatory categories including HLA loci, interferon signalling regulators, cytokine transducers, and innate immune sensors.

HLA class II alleles, such as HLA-DRB1*1104, DQA1*05:01, and DQB1*0301, has strong associations with diffuse cutaneous SSc (dcSSc) and anti-topoisomerase I antibodies (ATA), often linked to interstitial lung disease (ILD). Conversely, HLA-DQA1*02:01, DRB1*01, HLA-DRB1*04, HLA-DRB1*08 are mostly associated with limited cutaneous SSc (lcSSc) and anti-centromere antibodies (ACA).[Table .1] demonstrate that genetic association with SSc subtypes.

Table.1: Genetic association with SSc subtypes

Genes involved in dcSSc	Genes involved in lcSSc
HLA-DQA105:01, DRB11104	HLA-DQA1*02:01
IRF5 rs2004640, rs10488631	HLA-DRB1*01,*04, 8; DQB10501
STAT4 rs7574865	IRF8 rs11642873
TLR2 Pro631His	STAT4 rs7574865
MIF rs755622*C	IL6 rs1800795 (CG/GG)
IRAK1 rs1059702	TNFSF4 rs1234314, rs844648
IL6 rs1800795 (GG)	
TNFAIP3 rs5029939	

Among non-HLA genes, IRF5 and STAT4 are repeatedly associated with dcSSc, ILD, and cardiac involvement. IRF5 polymorphisms (rs2004640, rs10488631) enhance interferon signalling, promoting inflammation and fibrosis. STAT4 rs7574865 is associated with both dcSSc and severe organ involvement, including lung and cardiac fibrosis. [**Table.2**] shows that the Gene which involves in SSc organ fibrosis.

Table .2: Gene associated in SSc organ fibrosis

Organs	Genes Involved
Lung	IRF5, STAT4, IRAK1, TNFAIP3, MIF, IL6
Heart	STAT4
Kidney	HLA-DRB1, DQB1, STAT4, IRAK1
Skin	IRF8, IRF5, STAT3, IL6, MIF, TNFAIP3
GIT	IL6
PAH	MIF

IRAK1 and TNFAIP3 modulate inflammatory responses via NF-κB and TLR pathways, contributing to severe fibrosis. IRF8 may act as an antifibrotic regulator, while IL6 and MIF are linked to skin, lung, GI fibrosis, and PAH.[10] [**Table.3**] expressions Various Genes involve in function abnormality of SSc

Table.3 : Gene Functions in SSc

Gene/Signalling pathway	Function/ Mechanism
HLA Class I & II	Antigen presentation; determine autoantibody profile and SSc subtype
IRF5, IRF7, IRF8	Regulate type I IFN response; IRF8 has antifibrotic effects
STAT4	JAK-STAT signaling; Th1/Th17 pathway; linked to ILD, cardiac, renal, and ATA+
STAT3	Activated by IL-6 and TGF-β; promotes fibroblast activation
TYK2	Transmits IL-12/IL-23 signaling; risk SNPs linked to autoimmunity
IL6	Potent proinflammatory cytokine; causes endothelial injury and fibrosis
MIF	Enhances macrophage and fibroblast activation; linked to fibrosis and PAH
IRAK1	TLR/IL1R pathway → NF-κB activation; contributes to inflammation and fibrosis
TNFAIP3 (A20)	Inhibits NF-κB; loss of function variants increase fibrosis
TNIP1	Negative regulator of TNFAIP3; dysfunction increases inflammation
CD247	T-cell signaling adaptor; regulates T-cell activation
TLR2 (Pro631His)	Variant associated with ATA positivity and dcSSc; boosts inflammatory cytokines (IL6, TNFα)
IL12A, IL12RB1/2	Regulate Th1 response; variants associated with SSc and ILD
TNFSF4 (OX40L)	Co-stimulatory molecule; promotes T-cell survival and cytokine production

CLINICAL FEATURES: In lcSSc form is confined to the extremities, face and neck, where as in dcSSc there is generalized skin involvement and rapid progressive internal organ involvement [**Figure.1**][11] Woman between the age of 30- 50 years are mostly affected and has a low prevalence. The most frequently affected areas are the oral and perioral tissues. The clinical signs start with facial skin hardening and tongue rigidity, which gives the appearance of a mask. Similarly, where the nasal alae are atrophied, the nose seems constricted, giving the impression of a mouse facies. Temporomandibular joint can also be affected resulting in pseudoankylosis. Other internal organ manifestations are also evident in case of dcSSc.[12] SSc sine scleroderma, which makes up less than 1% of instances, is a disease in which some patients have no skin involvement.[13] Raynaud's phenomenon is observed in more than 90% of the patients. 97% sensitive and 98% specific criteria [**Figure.2**] for SSc were established by the American College of Rheumatology. To diagnose it as SSc, either the major criterion or two of the three minor criteria must be met.[11] **Figure .3** expressed various common clinical and radiological features od SSc. Some patients with SSc have no skin involvement and the condition is termed as SSc sine scleroderma and it accounts for less than 1% of cases.[13]

Figure .1 represent various systemic involvement of SSc

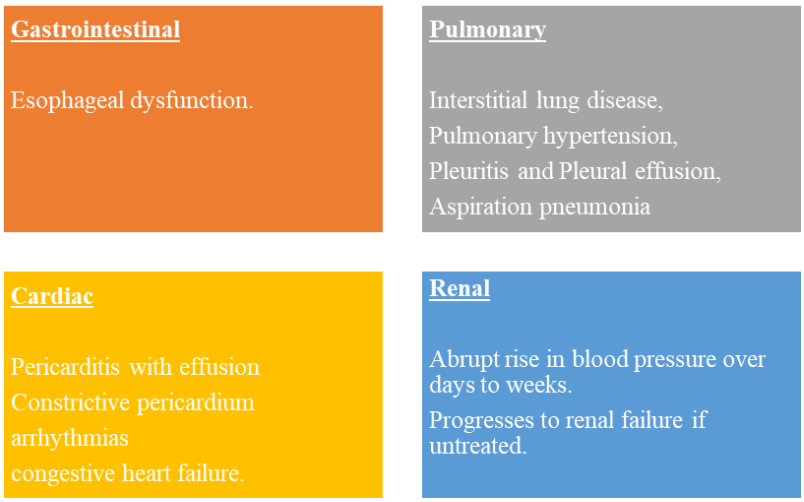


Figure .2 shows diagnostic criteria for SSc

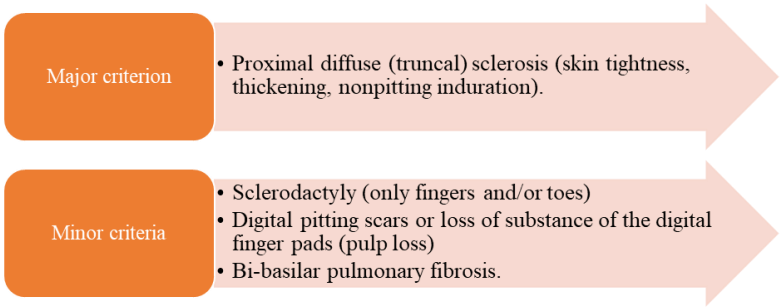
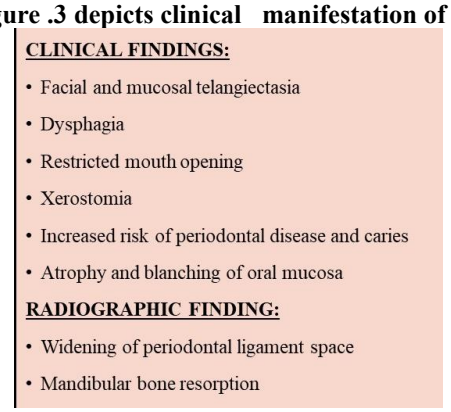


Figure .3 depicts clinical manifestation of SSc



DIFFERENTIAL DIAGNOSIS: Many conditions can cause diffuse thickening of the skin. While SSc being the major cause of cutaneous sclerosis, other conditions can also mimic SSc clinically and are known as scleroderma like syndromes. They are categorized based on their etiology as follows,

- **Inflammatory:**

POEMS syndrome
Graft versus host disease
Lichen sclerosus et atrophicus
Eosinophilic fasciitis

- **Deposition disorders:**

Nephrogenic systemic fibrosis
Scleromyxoedema

Scleroderma
Systemic amyloidosis

- **Metabolic:**

Hypothyroidism
Phenylketonuria

- **Genetic:**

Stiff skin syndrome
Werner's syndrome
Huriez syndrome
Winchester syndrome

- **Paraneoplastic Condition: Oral submucous fibrosis**
- **Others:**

Occupational exposure to polyvinyl chloride, silica, epoxy resins
Chemicals like benzene, toluene, naphthalene
Pharmaceuticals like bleomycin, d-penicillamine, l-tryptophan, toxic oil syndrome.
Many of these conditions are extremely rare or can be identified through associated clinical features. If the patient suspected of SSc does not show Raynaud's phenomenon, lacks typical nailfold capillaroscopy changes, tests negative for antinuclear antibodies (ANA), then the clinician should consider the following differential diagnosis list below in the [**Table .4].**[14,15]

Table.4 :displays Differential Diagnosis of SSc

DISORDER	LABORATORY	RAYNAUD'S PHENOMENON	NAILFOLD CAPILLARIES
Scleroderma	ANA, anti- centromere, anti- topoisomerasel, anti-RNA polymerase III	Present	Abnormal
Eosinophilic Fascuitis	Eosinophilia, Hypergammaglobulinemia, elevated aldolase	Uncommon	Mostly normal
Lichen sclerosus et atrophicus	None	Absent	Normal
POEMS syndrome	IgG or IgA monoclonal gammopathy	Present	Normal
GvHD	Anti-Scl, anti-PM- Scl, aPL, ANCA	Absent	Can be abnormal
Nephrogenic systemic fibrosis	Elevated serum creatinine	Absent	Normal
Scleromyxedema	Monoclonal gammopathy (IgG lambda), paraproteinemia	Uncommon	Normal
Scleredema	Monoclonal gammopathy (IgG kappa), hyperglycemia	Absent	Normal
Porphyria cutanea tarda	High level of porphyrin in urine and plasma	Absent	Normal
Phenylketonuria	High level of phenylalanine metabolites in blood, decrease level of tyrosine in the blood	Absent	Normal
Diabetic Chieroarthropathy	ICA. IAA, anti-GAD, hyperglycemia	Absent	-
Paraneoplasmatic Syndrome	Increased daily excretion of 5- HIAA	-	-

OVERLAP SYNDROME: Autoimmune conditions involving at least two connective tissue diseases are known as overlap syndromes. Systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis or polymyositis, and Sjogren syndrome are the most frequent combinations. Sometimes there are three or more overlapping autoimmune disorders, or other non-rheumatic autoimmune diseases, such as vitiligo, autoimmune thyroiditis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune thrombocytopenia, or celiac disease.[16]

INVESTIGATIONS: The main goals of the patient with a suspected case of systemic sclerosis are to confirm the clinical diagnosis and provide proof of the degree of visceral involvement. Certain histories like Raynaud's phenomenon, Skin thickening, Musculoskeletal symptoms like pain, stiffness. Diagnostics can occasionally be aided by occupational history of exposure to silica and industrial chemicals, which might be significant environmental triggers. Complete physical

examination should be performed. Digital pitting, ulcers, enlargement of nailfold capillaries, presence and extent of skin thickening should be monitored.[11] Routine screening of all the organ systems should be part of a thorough baseline description of SSc cases and repeat the test for early detection of organ-based disease.[**Figure.4**] [13] One important prognostic sign that should be used to track the extent of skin thickening is the modified Rodnan skin score. A higher skin score is associated with a higher death rate and a higher likelihood of internal organ involvement.[11]Recent years have seen a major evolution in SSc diagnoses, driven by improvements in imaging methods and serological markers [**Figure.5**]. Autoantibody profiling, especially antinuclear antibodies (ANA) and scleroderma-associated autoantibodies, helps in identifying the subset and predicts the disease progression. Additionally, more recent imaging techniques such as optical coherence tomography and high-frequency ultrasonography allow for the early identification of internal organ involvement and skin fibrosis.[17]

Figure .4: depicts investigation for various organs involvement

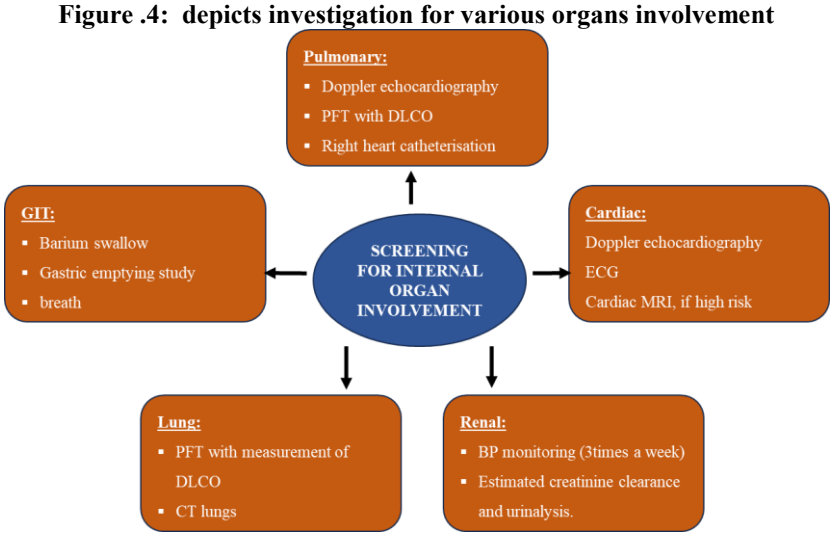


Figure .5: represent correlation of Immuno-fluorescence pattern & clinical presentation

ANTIGEN	IMMUNOFLUORESCENCE PATTERN	CLINICAL ASSOCIATION
Topoisomerase 1 (Scl-70)	Nuclear (diffuse fine speckles)	Although typical of diffuse skin involvement, occurs in both subsets of SSc and strongly associated with lung fibrosis
RNA polymerases I and III	Nucleolar (punctate)	Associated with diffuse skin involvement and especially with renal involvement. Can occur in limited subset
Fibrillarin (U3-RNP)	Nucleolar (clumpy) staining coilin bodies	Occurs in both major subsets. Associated with poor outcome in dcSSc with cardiac disease, pulmonary hypertension, renal involvement and myositis.
U1 RNP	Speckled antinuclear	Higher frequency in Afro-Caribbean patients with SSc. Associated with joint involvement and lung fibrosis in SSc.

ROLE OF ORAL HISTOLOGY: The hallmarks of systemic sclerosis histology include subepithelial fibrosis that spreads into fat and superficial and spontaneous inflammation surrounding the blood vessels. These symptoms closely resemble those of advanced submucous fibrosis. Despite having similarities to systemic sclerosis, they can be easily separated based on immunological and clinical results. The facial skin, not the oral mucosa, is affected in scleroderma, which results in trismus.[12]

SKIN HISTOLOGY AS DIAGNOSTIC MARKER: Laboratory results, physical examination, and history are typically used to make the diagnosis of SSc. Despite being excluded from the American College of Rheumatology's SSc classification criteria, skin histology aids in confirming the diagnosis and distinguishing SSc from other disorders that have similar clinical symptoms. The histological characteristics of SSc include sclerotic collagen bundles, increased epidermal thickness, loss of hair follicles and periadnexal fat, and compression of pilosebaceous units with few plasma cells and lymphocytic infiltration. Immunohistochemical markers such as α-SMA (alpha-smooth muscle actin) and CD34

assess the fibroblast activity in SSc. α-SMA highlights myofibroblast activation, while loss of CD34+ dermal dendritic cells indicates fibroblast transition into a profibrotic phenotype. These changes correlate with the degree of skin thickening and fibrosis.[18]

MANAGEMENT:

Appropriate diagnosis and staging of the disease are pre-requisites for effective treatment. Therapeutic strategies for SSc are multifaceted. It targets the immune dysregulation, vascular abnormalities, and fibrotic processes. Monoclonal antibodies such as transforming growth factor-β (TGF-β) and interleukin-6 (IL- 6), small-molecule inhibitors like tyrosine kinase inhibitors, limits the collagen deposition and prevents disease progression. Stem cell therapy, cell ablation and gene editing techniques regenerate the damaged tissue and halts the fibrotic processes. Newer diagnostic methods, like biomarkers and gene expression profiling, identify individuals at high risk for developing progressive disease and intervene proactively. Moreover, patient-tailored therapeutic management, which employs combination of immunosuppressive agents and targeted anti-fibrotic therapies, are investigated to improve treatment efficacy. Though systemic sclerosis (SSc) carries high morbidity and mortality, advancements in treatment leads to improved quality of life and increased survival.[11,17]

CONCLUSION: This review concludes that SSc is a complex disease with multiple cellular and molecular biomechanisms, deep phenotyping of new patients, clinical and antibody profiling, tissue sampling and individual patient evaluation could be implemented. These approaches could help in differentiating the others fibrotic conditions and at the earliest stages of the disease, the emphasis moves from treating organ-based problems to offering individualized therapies.

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