

## Systemic Sclerosis : A case report and review of current advances in treatment

**Abstract-**Systemic sclerosis(SSc) is a chronic multisystem disease characterized by excess deposition of connective tissue in skin and internal organs, associated with microvasculature changes and immunologic abnormalities.

We hereby report a case of scleroderma in a 52 year old female with classical clinical and histopathological findings. The latter part of this article discusses and reviews existing and novel emerging therapies for the treatment of SSc, with an emphasis on recent trials targeting the cutaneous and pulmonary manifestations of this disease.

**Key Word:** Scleroderma , Systemic Sclerosis, Chronic Multisystem Disease, Immunologic Abnormalities

**Introduction-** “Systemic sclerosis is a rare connective tissue disorder with unknown and complex pathogenesis. Systemic sclerosis can be divided into two forms, localized Scleroderma (morphea, linear scleroderma, and scleroderma en coup de sabre), or Systemic sclerosis, which can further be classified as either limited systemic sclerosis (formerly known as the CREST syndrome) or diffuse systemic sclerosis based on clinical and serological criteria”.<sup>1</sup>

“The pathogenesis of systemic sclerosis is complex and includes vascular alterations, immunological dysregulation, and extensive tissue fibrosis”.<sup>2</sup> “However, the trigger of this early putative vascular injury remains elusive. Ineffective angiogenesis, which can be assessed using nailfold capillaroscopy, is clearly apparent in scleroderma. A critical imbalance between factors promoting vasoconstriction (e.g., endothelin) and vasodilation (e.g., nitric oxide) is a key factor promoting vascular changes. Subsequent to vascular injury and immune disturbances, activated fibroblasts result in the excess deposition of extracellular matrix, which includes collagen, resulting in organ dysfunction and tissue fibrosis”.<sup>3</sup>

“Limited cutaneous systemic sclerosis(LcSSc), formerly known as the CREST syndrome, is associated with skin thickening distal to the elbows, distal to the knees, and/or face without trunk involvement. Diffuse cutaneous systemic sclerosis(DcSSc) is associated with skin thickening that may involve skin proximal to the elbows, proximal to the knees, face, and/or trunk.

Antinuclear antibodies (ANA) may be present in more than 90% of cases of systemic sclerosis, and at least one of the more specific autoantibodies (anti-centromere, anti-SCL70, and anti-RNA polymerase III) is present in up to 70% of the cases. The organs most frequently affected by scleroderma are the skin, gastrointestinal tract, lungs, kidneys, skeletal muscle, and pericardium”.<sup>(4,5,6)</sup>

## **Case report-**

A 52 year old female, who is a farmer hailing from Thiruporur, presented to our OPD with complaints of thickening of skin over the hands and tightness of skin over the face for 6 months. She was apparently normal 6 months back following which she developed thickening of skin, first over the distal part of her fingers, which were initially pruritic and edematous, then gradually extending proximal to the metacarpophalangeal joints. It was associated with difficulty in joint movement.

She also complained of skin tightness over the face, which was of gradual onset initially involving the perioral area, which was associated with difficulty in opening her mouth. There was history of occasional episodes of skin discoloration associated with pain on exposure to cold temperatures over the fingers, suggestive of Raynaud's phenomenon. Patient gives a history of painful ulcers and whitish hard raised lesions present over fingers. She also claims to have decreased sweating over hands. Occasional episodes of myalgia were observed. She denied a history of fever, breathlessness, dry cough, chest pain or palpitations. There was no history of nausea, constipation, diarrhoea, regurgitation, abdominal bloating or discomfort. She denies a history of oliguria, swelling of feet, swelling around eyelids or frothy urine. Nil history of headache, visual disturbances or seizures. She also did not give a history of grittiness in eyes, tingling or numbness over extremities, photosensitivity, rash over face or oral ulcers. There was no history of drug intake or previous treatments for the present condition. She is not a known case of diabetes, hypertension, tuberculosis or bronchial asthma. Patient did not have a history of any drug allergy or past surgical history. The patient did not report any similar complaints in the family.



Fig-1: Taut facial skin with induration



Fig-2: Perioral rhagades giving a purse string appearance



Fig-3 a



Fig-3 b

Fig.3a and b: Puffy fingers extending proximal to the metacarpophalangeal joint



Fig-4: Pitted scar over tip of the right middle finger



Fig-5: White chalky deposits over the dorsum of right middle finger

On examination, patient was conscious and well oriented. Vitals were stable. General examination was normal. No significant findings on systemic assessment. On cutaneous examination, the patient's facial skin was taut with induration(Fig-1). Ingram sign was positive. Perioral rhagades were present, giving a purse string appearance(Fig-2). On examination of the hands, Sclerodactyly extending proximal to metacarpophalangeal joints on both hands present(Fig-3a and b). Pitted scar was present at the tip of right middle finger(Fig-4). Loss of hair over all fingers was noted. Calcinosis cutis was present over the right middle finger(Fig-5) and left index finger. Flexion deformities were absent and there was no loss of pulp of finger. Nil significant nail fold changes were observed. Tendon friction rubs were absent. Raynaud's phenomenon was clinically elicited. Onycholysis, fissuring over palms and soles and dental caries present on further examination. Routine hematological tests were done, hemoglobin was 11.3g/dl, TC-6300cells/micro L, differential count- neutrophils-62.6%, eosinophils-4.5%, monocytes-6%, basophils-0.45, lymphocytes-26.5%. chest Xray had no significant findings. RFT was done, serum creatinine was 0.84mg/dl and blood urea nitrogen was 12mg/dl.

Fasting sugars was 82mg/dl and postprandial sugars was 103mg/dl.

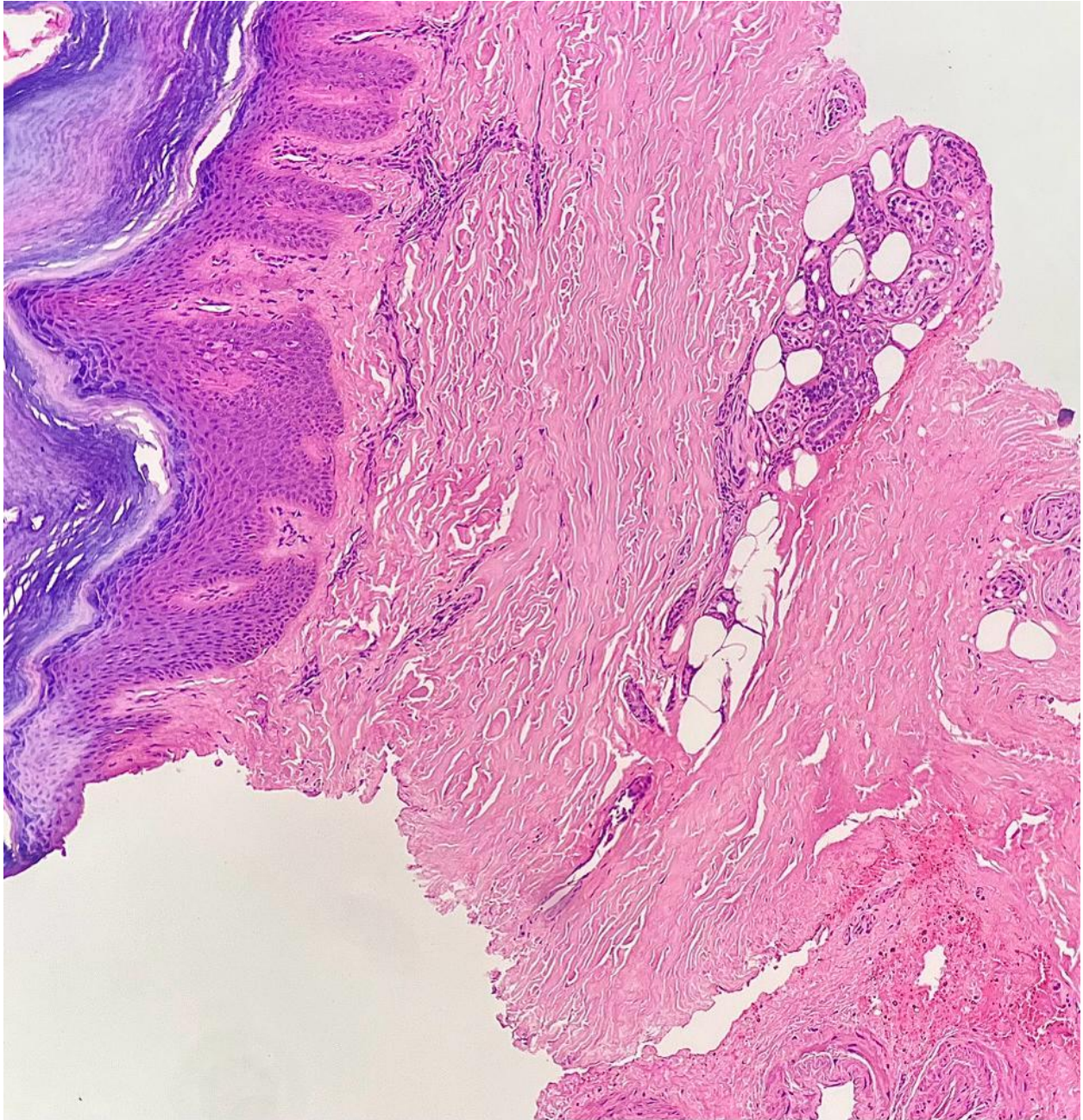


Fig-6: H&E staining showing hyperkerstosis, hypergranulosis and acanthosis of epidermis.  
Thick, compact, homogenous and hyalinised collagen bundles in the dermis

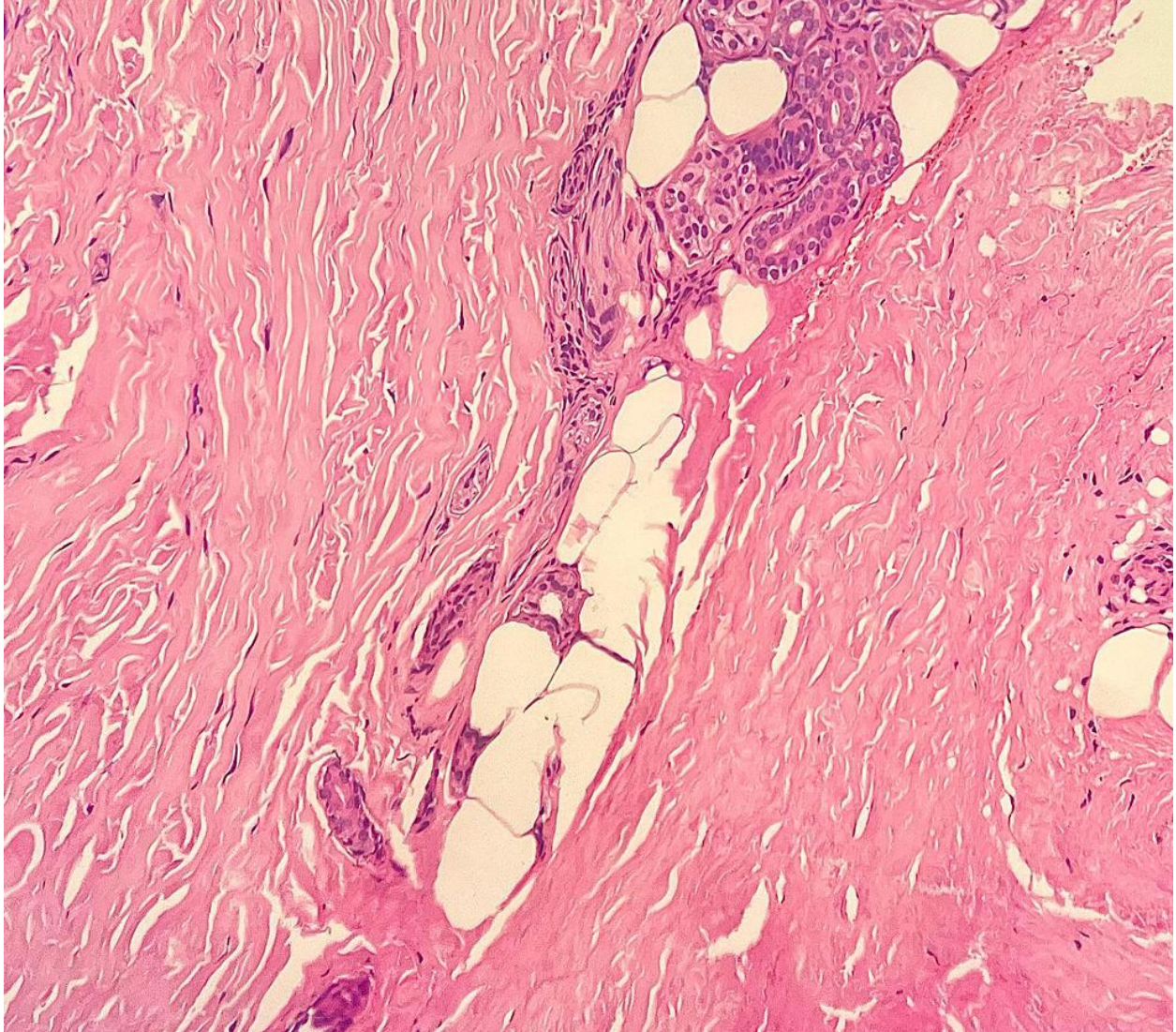


Fig-7: H&E staining showing collagen formation below subcutaneous tissue

Skin biopsy sample was obtained from the right middle finger which on examination revealed, hyperkeratosis, hypergranulosis and acanthosis of the epidermis. Dermis showed thickened compact homogenous hyalinised collagen with absent eccrine glands. Collagen bundles were present below the sub cutaneous tissue. Based on the above findings, a diagnosis of systemic sclerosis of limited type was made. Patient was started on Sildenafil, NSAIDS and Vitamin E supplements. Patient is under regular follow up.

#### **Discussion-**

“Systemic sclerosis is a rare connective tissue of unknown etiology that carries the highest case specific mortality among systemic rheumatic disorders”.<sup>7</sup>

“While pathologic vasculopathy, immune system dysregulation and fibrosis majorly contribute to organ destruction, there are significant differences in the phenotypic manifestations, rate of disease progression and response to treatment among patients. Historically, scleroderma renal crisis (SRC) carried the highest risk of mortality, however in recent times systemic sclerosis related interstitial lung disease(SSc-ILD) and pulmonary hypertension(SSc-PH) are leading causes of death. Recent data suggests that improvements in early detection of ILD and PH, along with the discovery of novel therapeutics for these complications has led to better survival”.<sup>8,9</sup>

“Treatment of SSc can be challenging owing to its rarity and heterogeneous disease manifestations. Treatment should be initiated to target active organ-specific complications of disease with a preference for therapies that may target more than one active organ system or target overlap connective tissue disease, if present”.<sup>20</sup>

### **Current therapies for Cutaneous systemic sclerosis:**

Cutaneous sclerosis is the cardinal symptom of systemic sclerosis and is present in most patients, either in a diffuse or limited distribution. Most clinical trials have focused on the early diffuse type, in which immunomodulatory therapy may serve to reverse and minimize disease burden.

“Randomized controlled trials (RCTs) have demonstrated that cyclophosphamide<sup>10</sup>, mycophenolate mofetil(MMF)<sup>11</sup> and hematopoietic stem cells(HSCT)<sup>12</sup> are associated with a statistically significant improvement in cutaneous sclerosis”. In general, mycophenolate mofetil, is considered first line therapy owing to its minimal toxicity and side-effect profile when compared to cyclosporine. Stem cell transplantation is generally reserved for patients with severe diffuse systemic sclerosis non responsive to immunomodulatory therapy given its high morbidity and mortality, although this approach can lead to the most dramatic improvement in cutaneous sclerosis.

### **Current therapies for Interstitial lung disease in Systemic sclerosis:**

“The complication of interstitial lung disease in systemic sclerosis is identified as the leading cause of disease-related mortality; however, review of contemporary literature suggests improved survival among these patients is due to more effective monitoring and treatment”.<sup>9</sup>

“Two landmark clinical trials, SLS-I<sup>10</sup> and SLS-II<sup>11</sup>, concluded cyclosporine and mycophenolate mofetil as disease modifying therapies for systemic sclerosis patients with active interstitial lung disease. These drugs were also associated with improvements in radiographic fibrosis and self-reported dyspnea”<sup>13</sup>. “Given its favorable tolerability and side effect profile, MMF is currently considered first-line therapy for patients with interstitial lung disease. For patients with progressive systemic sclerosis refractory to immunosuppressive therapy, autologous hematopoietic stem cell transplant may be considered”.<sup>10</sup>

“Nintedanib inhibits intracellular tyrosine kinase and fibroblast growth receptor (FGFR) . In a study conducted on 576 patients with interstitial lung disease, nintedanib slowed the rate of decline of lung function compared to the placebo. Patients who were taking mycophenolate mofetil at baseline and randomized to nintedanib had the slowest decline in lung function; Currently, more data is needed to determine when anti-fibrotic therapy should be initiated in patients with systemic sclerosis interstitial lung disease”.<sup>14</sup>

“Tocilizumab is a humanized monoclonal antibody that functions as an antagonist of the IL-6 receptor, thereby blocking its downstream effects. IL-6 is a pro-inflammatory cytokine that is frequently overexpressed in systemic sclerosis, promoting inflammation and profibrotic effects via the Janus kinase (JAK) 2/signal transducer and activator of transcription protein (STAT) 3 pathway”.<sup>20</sup> “A phase III trial was conducted with patients receiving either tocilizumab 162 mg subcutaneous weekly or placebo. Data concluded that tocilizumab stabilized lung functional vital capacity and is now FDA approved for systemic sclerosis interstitial lung disease. However, it is unknown whether tocilizumab can be safely combined with existing immunosuppressive treatments”.<sup>15</sup>

### **Emerging therapies for systemic sclerosis:**

A number of novel therapeutic agents have been recently studied for the treatment of systemic sclerosis. While some of these drugs, like lenabasum, abatacept, and riociguat, have failed to demonstrate treatment benefit, several new agents are currently under investigation.

“Rituximab is a humanized chimeric anti-CD20 monoclonal antibody that depletes peripheral B cells through antibody-dependent cell-mediated cytotoxicity. A meta-analysis of 24 articles concluded that rituximab improves Modified Rodnan score, quality of life and may effectively stabilize internal organ involvement”.<sup>16</sup> A small RFT conducted in Japan<sup>17</sup> showed that Rituximab improved the Modified Rodnan Score significantly and was well tolerated. It demonstrated treatment benefit regardless of disease duration or sub type. Patients had improved lung functional vital capacity and experienced significant radiographic improvement in the percent of lung fields occupied by interstitial changes. Based on current clinical data, rituximab offers a promising role in treating both cutaneous sclerosis and interstitial lung disease.

“In systemic sclerosis, endothelial injury initiates activation of T cells, which differentiate into T-helper type 2 response with subsequent release of interleukin-4 and interleukin-13. Romilkimab is a humanized IgG4 antibody that binds and neutralizes IL-4/IL-13, halting the promotion of fibrosis. In a recent study<sup>18</sup>, 97 patients having diffuse systemic sclerosis were treated with romilkimab or placebo for 24 weeks with or without background immunosuppressive therapy”.<sup>20</sup> There was a trend towards improvement in patients treated with romilkimab when compared to the placebo group. While these findings are encouraging, a phase III trial is needed as prior candidate treatments for dcSSc that showed promising phase II trial data, ultimately failed to demonstrate a treatment benefit in the phase III trial.

“Mesenchymal stromal cells contain immunomodulatory, proangiogenic, and antifibrotic therapeutic benefits and represent a novel intervention for patients with systemic sclerosis. In a study<sup>19</sup>, 20 patients were treated with bone marrow derived mesenchymal stromal cells and showed improvement in Modified Rodnan score with satisfactory safety and tolerability during study and follow up”. Unlike hematopoietic stem cells, which is associated with high risk of complications and mortality, mesenchymal stromal cells may represent a safer option for treating severe diffuse systemic sclerosis. Future studies are needed to understand which patients may benefit from this therapeutic strategy over conventional immunosuppression.

### **Conclusion-**

Systemic sclerosis is still undoubtedly a challenge for clinicians, because of the variety of symptoms. It is characterized by a severe course and high risk of early death. Scleroderma prognosis depends on the clinical picture and character of organ involvement, especially kidney, heart and lungs. As the pathogenesis of systemic sclerosis is still unclear, the treatment is based on disease-modifying and organ-specific drugs. Therapeutic decisions should be made after appropriate assessment of symptoms, disease duration, activity and complications. A number of new therapies are currently available to treat cutaneous and pulmonary manifestations of systemic sclerosis. Future studies are needed to understand whether combining therapies leads to enhanced outcomes and to develop refined strategies for personalizing treatment for patients based on molecular profiling.

### **Ethical Approval:**

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

### **Consent**

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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