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## A case of ANA-negative systemic sclerosis treated with methylprednisolone

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## Case Report

# **A case of ANA-negative systemic sclerosis treated with methylprednisolone**

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## **Abstract**

**Background:** Systemic sclerosis is a multi-systemic disease characterized by excessive fibrosis, inflammation, and vasculopathy. Common clinical features include skin thickening, telangiectasias, salt and pepper skin, beak-shaped nose, and microstomy. We report a case of ANA-negative systemic sclerosis in a male patient.

**Case illustration:** Our patient presented with a 10-month history of diffuse hyperpigmentation, skin tightening and decreased mouth aperture, accompanied by digital ulcers, hypopigmented macules and violaceous discoloration of the digits upon exposure to cold temperature. Punch biopsy done revealed mild acanthosis of the epidermis with basal cell layer hyperpigmentation, vacuolar alteration and thickening of the basement membrane zone. ANA was negative. Anti-Scl70 was positive. Patient was treated with methylprednisolone which was tapered over a course of 1 month, with noted decrease in tightening of the skin. Digital ulcers and discoloration of digits upon exposure to cold temperature were no longer observed.

**Discussion:** Diagnosis of systemic sclerosis is made on the presence of scleroderma proximal to the metacarpophalangeal joints, with two of the following minor criteria: sclerodactyly, digital ulcerations or bibasilar pulmonary fibrosis, as well as symptoms involving other organ systems; musculoskeletal, gastrointestinal, respiratory, cardiac, and renal.

**Conclusion:** While the presence of certain distinct features are needed in the diagnosis of systemic sclerosis, a distinct subset of the disease may be ANA-negative and may correspond to better prognosis. A thorough physical and diagnostic examination is needed in order to provide the optimum treatment for each patient. This would prevent systemic complications and further progression of the disease.

**Keywords:** *systemic sclerosis, diffuse hyperpigmentation, methylprednisolone, ANA-negative*

## **Background**

Systemic sclerosis (SSc) is a chronic, multisystem connective tissue disease with characteristic clinical manifestations.<sup>1</sup> Common clinical features include skin thickening, telangiectasias, salt and pepper skin and typical facial features such as a beak-shaped nose and microstomy. Systemic sclerosis is caused by inflammation and fibrosis involving skin and internal organs due to microangiopathy. It is divided into diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc) forms based on the extent of skin involvement. Pathologic features of SSc include microvascular damage, dysregulation of adaptive and innate

immunity, and fibrosis that can involve the skin, heart, lungs, kidneys, gastrointestinal tract and other organs. Clinical outcome is determined mainly by the rate of progression and extent of organ fibrosis are the primary determinants of clinical outcome.<sup>1</sup>

Early diagnosis of SSc, and assessment and treatment of organ involvement, are of utmost importance in patient management. Organ involvement is responsible for most of the complications and mortality in SSc. Observation of certain clinical signs may facilitate early diagnosis and identify organ involvement.<sup>2</sup> Diagnosis of systemic sclerosis is made on the presence of scleroderma proximal to the metacarpophalangeal

joints, with two of the following minor criteria: sclerodactyly, digital ulcerations or bibasilar pulmonary fibrosis, as well as symptoms involving other organ systems such as musculoskeletal, gastrointestinal, respiratory, cardiac, and renal.

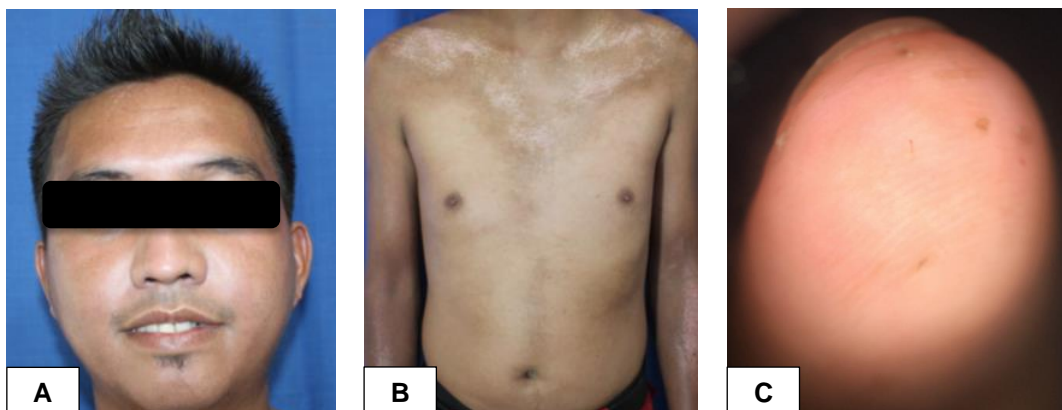
Although there are several treatment options, corticosteroids are still the mainstay of treatment for most autoimmune diseases. However, there is no randomized controlled study addressing the use of corticosteroids in SSc that demonstrates improvement of skin fibrosis or organ involvement.<sup>3</sup> A placebo-controlled study by Sharada et al. showed a significant improvement in the modified Rodnan total skin score (TSS) after patients were given intravenous (IV) dexamethasone pulse therapy in diffuse SSc.<sup>4</sup> It is known that the extent and severity of skin lesions, as well as the presence of cardiovascular, pulmonary, and renal manifestations determine the prognosis of the disease. However, presence of anti-nuclear

antibodies (ANA) may also represent a distinct subset of the disease.<sup>1</sup>

### Case Illustration

This is a case of a 24 year old male, cruise-ship waiter who presented with a 10-month history of diffuse hyperpigmentation, skin tightening and decreased mouth aperture, accompanied by hypopigmented macules and violaceous discoloration of the digits upon exposure to cold temperature. Past medical history and family medical history were unremarkable.

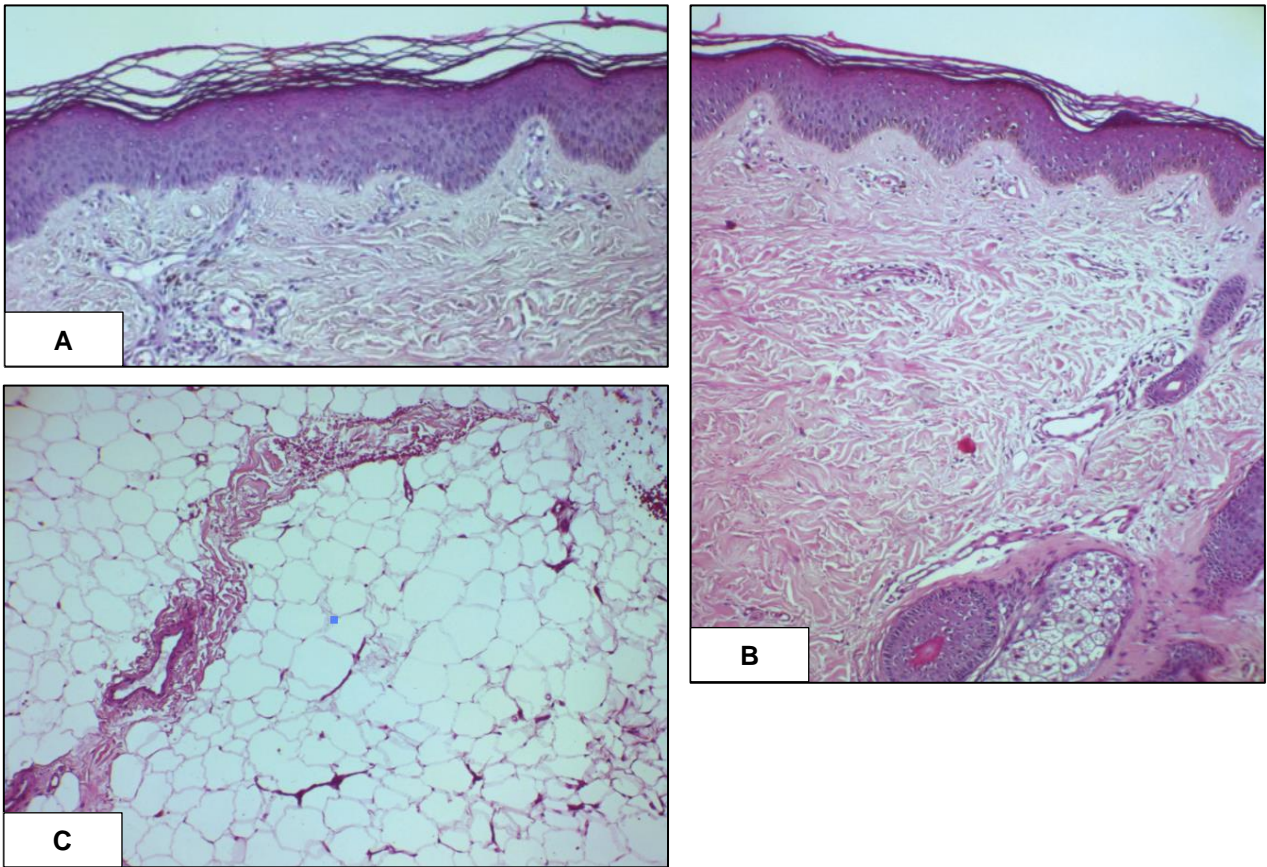
Dermatologic examination showed diffuse hyperpigmentation with hypopigmented macules on the face, neck, trunk, and extremities. There was noted tight, stiff, and shiny appearance of skin on face, trunk and extremities (Figure 1 A and B). There were shallow pitted scars on the digital pulps (Figure 1C). Decreased oral aperture noted. Clinical findings were consistent with scleroderma.



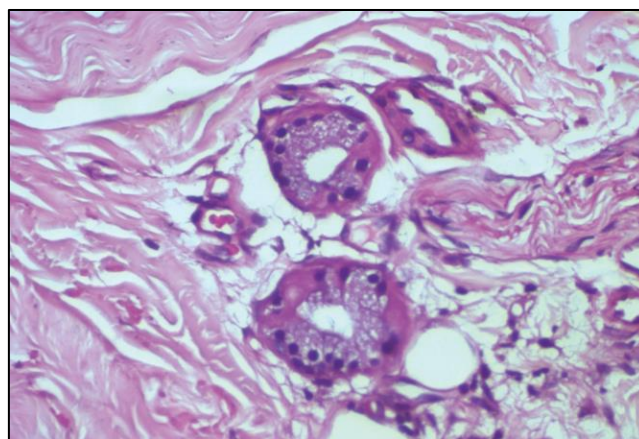
**Figures 1.** A and B. Tight, Stiff, and Shiny Appearance of Skin on Face, Trunk and Extremities; C. Shallow, Pitted Scars on the Digital Pulp

A 4 mm-skin punch biopsy was taken from a patch in the right arm. Histopathology showed mild acanthosis of the epidermis with basal cell layer hyperpigmentation, vacuolar alteration, and thickening of the basement membrane zone. The dermis showed fibrosis, extravasation of red blood

cells and a diffuse perivascular and periadnexal inflammatory infiltrate of histiocytes and lymphocytes. Part of the subcutaneous tissue is replaced by thick bundles of collagen. Biopsy result was consistent with scleroderma (Figure 2 and 3).



**Figure 2.** On Low Magnification Shows (10x); A. Mild Acanthosis in Epidermis; B. Dilated Blood Vessel and Mild Inflammatory Cell Infiltration Surrounded by Thick Collagen in Dermis; C. Replacement of the Subcutaneous Tissue with Thick Bundles of Collagen in Subcutis



**Figure 3.** On High Magnification (40x) of the Dermis, Histopathology Shows Eccrine Glands Surrounded by Broad, Sclerotic, and Strongly Eosinophilic Collagen Bundles

The patient was referred to a rheumatologist with frequent follow-up consultations at our institution. ANA was negative. ESR and Scl 70 antibody were

elevated, suggesting Systemic Sclerosis. The patient was given oral methylprednisolone tapered over a course of one month, starting at a dose of

0.8 mg/kg/day for 7 days, then 0.6 mg/kg/day for 7 days, 0.5 mg/kg/day for 7 days, 0.4 mg/kg/day for 7 days, then 0.3 mg/kg/day for 7 days. Patient was followed-up every week, with noted decreased skin tightening, as measured by the Modified Rodnan Skin Score (mRSS). Initial mRSS was a maximum score of 26 with global average score of 1.2. On the last follow-up, the maximum score was 21 and global average score was 1.0, with marked improvement in skin tightening of face and upper extremities. Decreased diffuse hyperpigmentation was also noted.

## Discussion

This is a case of a 24 year male, presenting with diffuse hyperpigmentation with hypopigmented macules on the face, neck, trunk, and extremities. There was noted tight, stiff, and shiny appearance of skin on face, trunk and extremities and shallow pitted scars on the digital pulps.

The patient was managed as a case of Systemic Sclerosis. Various factors are involved in the etiology and pathogenesis of the disease. SSc occurs more commonly in families with SSc (1.6%) than in the general population.<sup>5</sup> The presence of SSc in a first-degree relative may increase the risk of SSc, Raynaud's phenomenon (RP), interstitial lung disease, and other autoimmune diseases.<sup>6</sup>

There is also an association of SSc with occupational exposure to silica, polyvinyl chloride trichloroethylene, organic solvents, pesticides, hair dyes, and industrial fumes. Drugs have also been implicated in the development of SSc. Bleomycin, pentazocine, and cocaine are some of the drugs that have been identified. Radiation therapy has also been noted to cause *de novo* SSc and may also cause exacerbation of tissue fibrosis in patients with existing SSc.<sup>7</sup>

The modified Rodnan Skin Score (mRSS) is a tool to assess the extent and severity of skin sclerosis. It is recommended that mRSS to be calculated at least every 3 months. Published clinical trials have shown that mRSS usually does not have clinically meaningful changes ( $\geq 4$  points) in less than 3 months.<sup>8</sup>

The primary event in the development of SSc is vascular injury and activation. It was observed that vascular damage occurred prior to fibrosis. Vascular injury leads to endothelial cell activation and dysfunction. This facilitates increased expression of vascular endothelial cell adhesion molecule-1 and endothelial leukocyte adhesion molecule-1. There is also altered secretion of

vasoactive mediators, activation of platelets, and fibrinolytic pathways.<sup>9</sup> These events explain the occurrence of Raynaud's phenomenon, manifested as discoloration of the digits upon exposure to cold temperature and emotional stress. This was evident in our patient.

Meanwhile, the mechanism of diffuse pigmentation in SSc is unknown. Changes in Melanocyte-stimulating Hormone ( $\beta$ MSH) level do not cause pigmentation.<sup>10</sup> Increased production of cytokines, such as IL-1, was noted in SSc patients. These cytokines stimulates Endothelin-1 (ET-1) productivity from keratinocytes. ET-1 promotes melanogenesis by increasing melanocytes and melanin synthesis. Increased ET-1 productivity in keratinocytes and a correlation between ET-1 productivity in keratinocytes and skin pigmentation is seen in severe cases of SSc.<sup>11</sup>

There are no documented studies for treatment of pigmentary changes. Since ET-1 and vasoconstriction have been postulated as factors in pigmentation.<sup>11</sup> ET-1 antagonists and vasodilators may play a beneficial role.<sup>1</sup>

Organ involvement, such as cardiovascular, pulmonary, gastrointestinal, and renal involvements usually determine the severity and prognosis of the disease. However, a study by Salazar et al also demonstrated the importance of the presence of antinuclear antibodies in the prognosis and management of the disease; 6.4% from the study population, mostly males, were ANA-negative. It was later concluded that those patients had less vasculopathy but had more frequent lower gastrointestinal involvement. They further represented a distinct subset of the disease.<sup>12</sup>

In systemic sclerosis (SSc), little evidence for the effectiveness of anti-inflammatory and immunosuppressive therapy exists.<sup>3</sup> Steroids inhibit collagenase activity<sup>13</sup> but high-dose of steroid is associated with scleroderma renal crisis.<sup>3</sup> However, corticosteroids are still frequently prescribed due to its availability and affordability.

Methylprednisolone (MP) is derived from hydrocortisone. It is an intermediate acting, potent, anti-inflammatory agent. It has a biological half life of 12-36 hours. It is 1.25 times more potent than prednisolone and has a low tendency to induce sodium and water retention.<sup>14</sup> Hence, it was chosen as the drug of choice in our patient. Marked improvement in skin lesions were observed in our patient treated with methylprednisolone.

## Conclusion

Diagnosis of systemic sclerosis is made on the presence of scleroderma proximal to the metacarpophalangeal joints, with two of the following minor criteria: sclerodactyly, digital ulcerations or bibasilar pulmonary fibrosis, as well as symptoms involving other organ systems; musculoskeletal, gastrointestinal, respiratory, cardiac, and renal. A distinct subset of the disease may be ANA-negative and may correspond to better prognosis of symptoms of disorders in vasculopathy. A thorough physical and diagnostic examination is needed in order to provide the optimum treatment for each patient. Despite its availability and ease of use, prudent use of corticosteroids is still warranted.

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