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Late onset systemic sclerosis with seronegativity: a rare presentation of an uncommon disease

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SUMMARY

Systemic sclerosis (SSc) is an uncommon connective tissue disorder characterized by multisystem involvement with fibrosis of skin and internal organs. Antibody formation is one of the hallmarks of SSc. Antinuclear antibodies (ANA) are positive in 97% of patients with SSc. We report a rare case where the patient was negative for ANA, Anti-topoisomerase I, Anti-centromere and Anti-RNA polymerase III antibodies.

Key words: *Systemic sclerosis; antinuclear antibodies; anti-topoisomerase I.*

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INTRODUCTION

Systemic sclerosis (SSc) is an uncommon disease of complex pathogenesis with strong female predominance and peak age of onset at 30-50 years (1). The hallmarks of SSc are autoimmunity, inflammation, functional and structural alterations in small blood vessels, interstitial and vascular fibrosis in the skin and internal organs.

It affects skin and subcutaneous tissue in addition to internal organs such as lungs, heart, kidneys and gastrointestinal tract. It is broadly classified into diffuse cutaneous and limited cutaneous subsets based on the skin involvement, clinical and laboratory features. The early stages of disease may be dominated by inflammation and vascular injury, while fibrosis and vascular insufficiency are most prominent in advanced stages. Antinuclear autoantibodies (ANA) are present in almost all patients with SSc and can be detected at disease onset. Autoantibodies against topoisomerase I (Scl-70) and centromere are specific for SSc. While the majority of the patients have circulating antinuclear antibodies (90-95%), a few are ANA negative (2).

CASE REPORT

A 58-year-old female presented with chief complaints of darkening and thickening of the skin along with intermittent bluish discoloration of fingers and toes of all four limbs on exposure to cold for the last 2 years. Darkening and thickening of skin was insidious at onset, while bilaterally symmetrical, initially involved finger and toes of both upper and lower limbs and gradually progressed to involve both forearms and legs along with face, resulting in limitation of movement of joints of hands and feet. On examination, the pa-



Figure 1 - Maximum thickening on the fingers and toes.

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tient was conscious and oriented. She was thinly built with body mass index of 17.57 kg/m^2. Blood pressure was 120/70 mmHg, pulse rate was 76 min, respiratory rate was 14/min with oxygen saturation of 98% on room air.

On general physical examination, generalized darkening of skin was evident, which was maximum on the distal part of the limbs. The skin was dry and coarse, with loss of hairs and thickening which was maximum on the fingers and toes (Figure 1). There was painless, restriction of passive movement in joints of both hands and feet, along with restricted mouth opening. Systemic and gynecological examination was within normal limits.

On laboratory evaluation, complete hemogram, blood sugar, liver function tests and lipid profile were normal. Kidney function tests were abnormal with urea-106 mg/dL, creatinine-2.7 mg/dL and proteinuria of 425.6 mg/day. In thyroid profile, free T3, T4 were normal with raised TSH (9.61 uIU/mL) and anti TPO antibody (42.3 IU/mL). ANA, anti-topoisomerase I, RNA polymerase III and anti-centromere antibodies were negative. U1RNP antibody, anti-dsDNA and anti-Smith antibodies were also negative.

Chest X-ray, ECG and ultrasound (abdomen and pelvis) were within normal limits. Pulmonary function test was normal. 2-D ECHO revealed mild tricuspid regurgitation with mild pericardial effusion and evidence of pulmonary arterial hypertension (mPAP- 34 mmHg). High resolution computed tomography showed traction bronchiectasis and linear fibrotic bands in left lower lobe with mild bilateral pleural effusion (Figure 2).

Skin biopsy showed unremarkable epidermis, perivascular and adnexal mononuclear cell infiltrate in upper dermis with increase in collagen deposition extending from mid dermis to subcutaneous tissue on Masson's trichome staining (Figure 3).

On renal biopsy, two out of five glomeruli were sclerosed with remaining glomeruli showing increased mesangial matrix expansion, mesangial cell proliferation and capillary basement thickening. Tubules

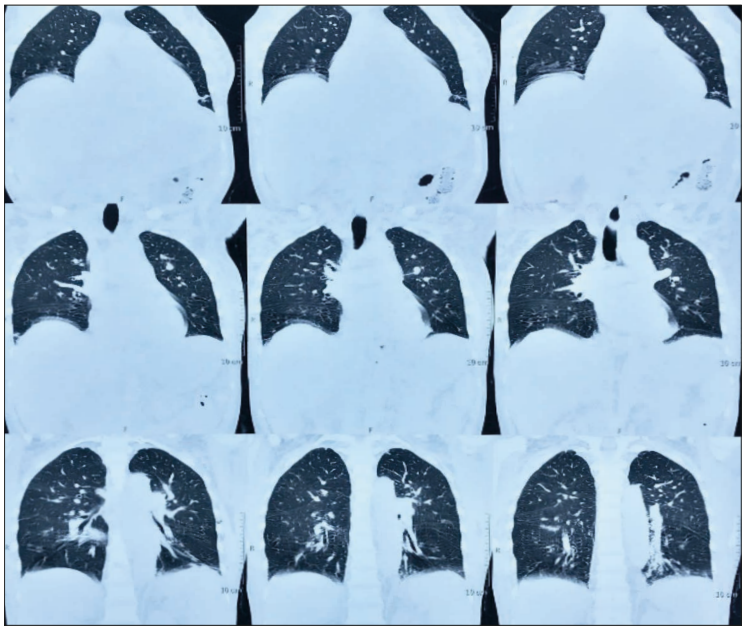


Figure 2 - High-resolution computed tomographic scan of the chest.

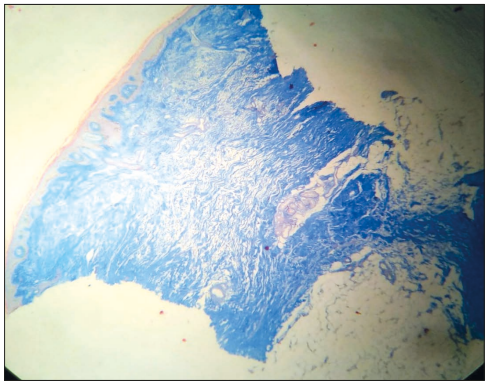


Figure 3 - Skin biopsy on Masson's trichome staining.

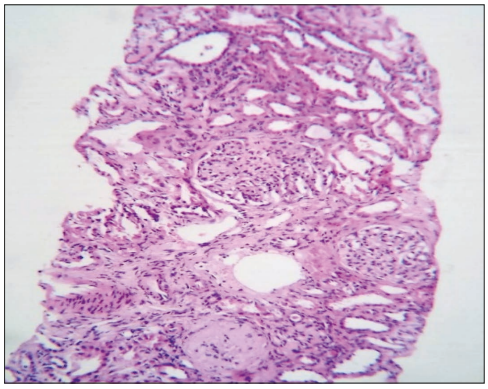


Figure 4 - Renal biopsy.

Table I - 2013 ACR/EULAR criteria for the classification of systemic sclerosis.

Item	Sub-item(s)	Score
Skin thickening of fingers of both hands extending proximal to metacarpophalangeal joints	–	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers Sclerodactyly of the fingers distal to metacarpophalangeal joints but proximal to proximal interphalangeal joint	2 4
Fingertip lesions (only count the higher score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension/ interstitial lung disease (only count the higher score)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	–	3
SSC-related autoantibodies (maximum score is 3)	Anti-centromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3

The total score is determined by adding the maximum scores in each category. Patients with total score of ≥9 are classified as having definite scleroderma.

showed basement membrane thickening with chronic mononuclear cells infiltration in the interstitium (Figure 4). The ACR/EULAR criteria score was 14 (greater than 9), including Raynaud's phenomenon (3 points), classical skin changes and biopsy (9 points) with evidence of pulmonary artery hypertension (2 points) on echocardiography. The total score was consistent with the diagnosis of SSc (Table I). The patient was started on aspirin, losartan and local application of nitroglycerine. On follow up, the patient experienced some relief in symptoms pertaining to Raynaud's phenomenon.

DISCUSSION

SSc and scleroderma-like syndromes are characterized by complex immune disorders, vascular damage and overproduction of the extracellular matrix by activated fibroblasts. Antinuclear antibodies against nucleolar antigens are characteristic of SSc, found in 97% of the cases. Specific autoantibodies such as anti-topoisomerase I, anti-centromere and anti-RNA polymerase (RNAP) have been implicated in disease pathogenesis by producing directly toxic or other proinflammatory effects. Anti-centromere antibodies are associated with Raynaud's phenomenon and CREST syndrome, being present in up to 98% of patients (3). In contrast, anti-topoisomerase I antibodies predict diffuse cutaneous disease, pulmonary fibrosis, association with cancer and cardiac involvement, as well as rapid disease activity with longer duration (4, 5). Anti-RNAP I and III antibodies are specific for SSc and associated with diffuse cutaneous SSc with renal crisis (6).

Autoantibodies are found in almost all cases of systemic sclerosis but can be negative in a few cases. It is possible that ANA-negative patients may have some other antibodies that are not currently detected by traditional assays. In a study conducted by Salazar et al., out of 3249 patients, 6.4% were ANA negative and they were less likely to have vasculopathic features of the disease (7). Hamaguchi et al. in their study reported that 5% of patients were ANA negative with low severity of skin involvement and rare incidence of pulmonary arterial hypertension and interstitial lung disease in ANA negative group (8).

ANA negativity may also point towards causes other than SSc, such as eosinophilia-myalgia syndrome, eosinophilic fasciitis, graft *vs* host disease, nephrogenic systemic fibrosis, scleredema, scleromyxedema, endocrine disorders, amyloidosis, exposure to chemotherapeutic agents or

organic solvents and patients with an underlying cancer. SSc and neoplastic disorders may coexist one with the other. In many cases it is necessary to differentiate whether SSc is idiopathic or if it is a paraneoplastic symptom.

Paraneoplastic sclerodermiform syndrome is suspected with a later age of onset, asymmetrical involvement, non-involvement of internal organs, unilateral Raynaud's phenomenon, association with RNA polymerase III antibody, a poor response to conventional treatment and a good response to the treatment of the underlying tumor with amelioration of symptoms and decrease or disappearance of antibody titers (9). It is important to rule out any malignancy in case of late onset of the disease with negative ANA and family or personal history of cancer. It is mostly found in patients with cancer of the stomach, ovary, breast and lungs (10).

Autoimmune thyroid diseases are known to accompany a number of autoimmune disorders, including pernicious anemia, type 1 diabetes mellitus, Addison's disease, celiac disease or immune thrombocytopenia. Although thyroid may be involved in SSc, various studies have documented its association with autoimmune hypothyroidism which was also seen in our case (11-15).

Fibrosis of the skin is the hallmark of SSc and collagen fiber accumulation is most prominent in the reticular dermis, which progressively invades the subjacent adipose layer. It is also accompanied by marked expansion of the dermis with obliteration of the hair follicles, sweat glands, sebaceous glands and other skin appendages. Similar findings were observed in our patient's skin biopsy. In the kidney, there is chronic renal ischemia secondary to vascular insufficiency resulting in sclerosis and shrunken glomeruli. On histology, tubular changes such as flattening and degeneration of tubular cells may occur. Alternatively, patients may present with scleroderma renal crisis showing features of thrombotic microangiopathy.

Although our patient presented late, *i.e*. at the age of 58 years, with negative autoantibodies, the bilaterally symmetrical involvement of skin, presence of pulmonary arterial hypertension, bilateral Raynaud's phenomenon, no evidence of underlying malignancy with ACR/EULAR score of 14 was consistent with the diagnosis of seronegative limited cutaneous SSc with autoimmune hypothyroidism.

CONCLUSIONS

Systemic sclerosis usually presents in females at reproductive age but in case of late presentation with atypical features of SSc, paraneoplastic and other causes of scleroderma should be ruled out before labelling the patient as a case of idiopathic systemic sclerosis.

REFERENCES

1. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009; 360: 1989-2003.
2. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther. 2003; 5: 80-93.
3. Reveille JD, Solomon DH. American College of Rheumatology Ad Hoc Committee of Immunologic Testing: Linee guida basate sull'evidenza per l'uso di test immunologici: anticorpi anticentromero, Scl-70 e nucleari. Arthritis Rheum. 2003; 49: 399-412.
4. Perera A, Fertig N, Lucas M, et al. Clinical subsets, skin thickness progression rate, and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. Arthritis Rheum. 2007; 56: 2740-6.
5. Hanke K, Dahnrich C, Bruckner CS, et al. Diagnostic value of antitopoisomerase I antibodies in a large monocentric cohort. Arthritis Res Ther. 2009; 11: R28.
6. Phan TG, Cass A, Gillin A, et al. Anti-RNA polymerase III antibodies in the diagnosis of scleroderma renal crisis sine scleroderma. J Rheumatol. 1999; 26: 2489-92.
7. Salazar GA, Assassi S, Wigley F, et al. Antinuclear antibody-negative systemic sclerosis. Semin Arthritis Rheum. 2015; 44: 680.
8. Hamaguchi Y, Hasegawa M, Fujimoto M, et al. The clinical relevance of serum antinuclear antibodies in Japanese patients with systemic sclerosis. Br J Dermatol. 2008; 158: 487-95.
9. Fam AG. Paraneoplastic rheumatic syndromes. Bailliere Best Pract Res Clin Rheumatol. 2000; 14: 515-33.
10. Butler RC, Thompson JM, Keat ACS. Paraneoplastic rheumatic disorders: a review. J R Soc Med. 1987; 80: 168-72.
11. Biro E, Szekanecz Z, Czirjak L, et al. Asso-

ciation of systemic and thyroid autoimmune diseases. Clin Rheumatol. 2006; 25: 240-5.
12. Antonelli A, Ferri C, Fallahi P, et al. Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis. Eur J Endocrinol. 2007; 156: 431-7.
13. Ghayad E, Tohme A, Haddad F, et al. Scleroderma with anomalies of the thyroid function. 7 cases. Ann Med Intern. 1997; 148: 307-10.
14. Tosti A, Peluso AM, Rapacchiale S, et al. Thyroid function in systemic sclerosis. J Endocrinol Invest. 1991; 14: 783-4.
15. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative Arthrit Rheum. 2013; 65: 2737-47.