Systemic sclerosis in two generations family: a mother and offspring

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Systemic sclerosis (SSc) is uncommon connective tissue disease characterized by a pathological thickening and tethering of the skin and involvement of internal organ (i.e gastrointestinal tract, heart, lungs, and kidneys). Systemic sclerosis seems to result from a multifactorial process (alteration of the immune system, genetic, and environmental factors) but its pathogenesis remains unclear. A familial history of SSc represents an important risk factor for developing the disease.[1] We describe two generations family who developed SSc.

CASE REPORT

Case 1

A 25 year old female visited Rheumatology outpatient units at Cipto Mangunkusumo Hospital, Jakarta with the chief complain of fingers turn blue when they are exposed to cold temperature, since three months prior to this visit. She also had swollen hands, fatigue, and arthralgias. Physical examination showed blood pressure of 90/70 mmHg, a regular heart beat of 84/min, and a temperature of 35.8°C, sclerotic plaque with macular hyperpigmentation in the scalp, pre-auricular, and anterior of the neck, and some teleangiectasias at the tip of the fingers. Her skin showed taut at face, hands, fingers, and feet, with the Rodnan skin score of 10. Cardiopulmonary examinations were within normal limit. Laboratory studies revealed a leukocyte count of 6.320/mm^3, hemoglobin of 14.1g/dl, platelet count of 398x$10^3$$mm^3$, and erythrocyte sedimentation rate (ESR) of 6 mm/h. Ureum 20/mm^3 and serum creatinine 0.5/mm^3 with a creatinine clearance rate (Ccr) of 102.2 ml/min (Cockroft-Gault formula). Urinalysis and electrolytes were normal. Other laboratory values were CRP 0.2mg/ml, Rheumatoid factor (RF) <8 (negative), antinuclear antibodies (ANA) test 14.32 (N <1), ANA profile showed positive Anti Scl-70 (+++), the others were negative. She underwent biopsy of the skin and the histopathology showed scleroderma (see figure 1). The electrocardiogram and chest X-ray were normal. She was diagnosed with diffuse cutaneous SSc based on New York criteria for the SSc. She was started with nifedipine 5 mg b.i.d, and methotrexate 7.5 mg/week, and folic acid. Interestingly, she informed that her mother has the same problem with her.

Case 2

Her mother; 46 year-old, was invited to our Rheumatology outpatient unit. She had chief complains of skin thickening on the face and the upper trunk since six months prior to that visit. Her fingers also changed color when they exposed to cold however she could not recall when it started. She had suffered from cough, fever, and fatigue for the last two weeks prior to visit Rheumatology Unit. She lives in the same house with her own daughter. Physical examination revealed sclerodactily, "salt and pepper" appearance in the posterior of the neck and upper trunk and the skin tautness with the Rodnan skin score of 19. On lung examinations, fine crackles were noticed from both lower lungs. Cardiac and abdominal examinations were normal. Laboratory studies revealed a leukocyte count of 5,230/mm^3, hemoglobin of 13.5g/dl, platelet count of 32.7x10^4 mm^3, and ESR 28mm/h. Urinalysis detected microscopic hematuria and leukocyturia without proteinuria and with a Ccr of 117.4 ml/min. Acid-fast bacteria from sputum examination was negative. Other laboratory values were CRP 8.1mg/ml, Complement C_3 0.97 g/L, and C_4 0.11 g/L. The RF level was 64 (positive). Anti SS-A, anti SS-B, anti Scl-70, anti dsDNA were all negative. Anti nRNP/Sm and anti CENP B were positive with high titer (positive +++). Anti Ro-52 and anti Sm were also positive. ANA was 14.55 (N<1). Chest X-ray revealed minimal infiltrates at both lungs. Electrocardiogram and echocardiogram were all normal. In a barium enema study of the esophagus, no delay was observed. She was also diagnosed as SSc with diffuse cutaneous type.

DISCUSSION

Antibody and genetic factor

Systemic sclerosis is uncommon connective tissue disease and its etiology is unknown. The genetic of SSc are complex, and the disease is believed not inherited in a straightforward mendelian fashion. Twins show a low rate of disease concordance (<5%).[2] The concordance of scleroderma in twins is 5.9%, roughly 300-fold that of chance alone.[3] This rate is similar between monozygotic and dizygotic twin pairs. However, one recent study analyzing the prevalence of the disease among monozygotic and dizygotic twin pairs revealed a quite low and similar concordance rate among identical and fraternal twins (about 4.7%), arguing for a

shared environmental rather than a genetic link.[4] Other studies have shown that SSc occurs significantly more frequently in families with SSc (1.6%) than in general population (0.026%). Although the absolute risk of SSc for each family member is low, a positive family history represents the strongest risk factor yet identified for SSc, indicating an important role for heredity in disease susceptibility. First-degree relatives of SSc patients also are more likely to have a positive antinuclear antibody than controls.[5] However, there is not an increased familial occurrence of more specific serologic features such as serum anticentromere antibody.[6]

In contrast to other connective tissue diseases, HLA linkages are generally weak in SSc. Particular HLA haplotypes do show associations with distinct serologically defined SSc subsets, however. A cluster of SSc cases had been described among Choctaw Native Americans living in Oklahoma, with affected individuals sharing a unique American Indian HLA haplotype (B35, Cw4, DRB1*1602[DR2], DQA1*0501, and DQB1*0301 [DQ7]).[4,6] Report from Asia showed that DRB1*0101, *0405, and *1302 alleles were associated with high anticentromere antibody titers in the Japanese population.[7]

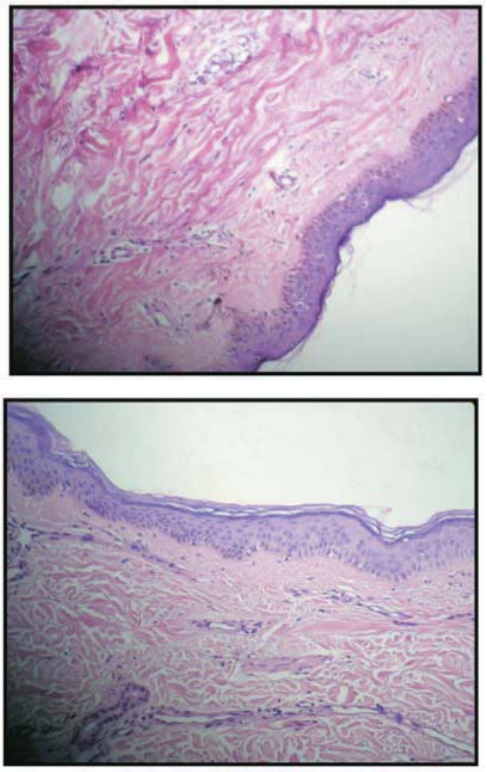

Figure 1 Skin biopsy of patient 1 (above) and patient 2 (below). Dermis consists of fiber tissue with parallel bundle showing paucity of skin adnexal glands.

Current investigations in SSc genetics focus primarily on polymorphisms in candidate genes. Associations of specific single nucleotide polymorphism have been reported in genes involved in immunity and inflammation, vascular function, and connective tissue homeostasis.

Significant serologic heterogeneity is well known to occur in SSc. Although it remains controversial whether autoantibodies seen in patients with SSc have an actual role in pathogenesis, these serologic markers are useful in the diagnosis and clinical management of scleroderma patients. Anti-U1-RNP antibodies are usually seen in association with CTD overlaps, specifically with Raynaud's phenomenon, joint involvement, myositis, lcSSc, and a more favorable outcome.[8]

The antibodies of our patients showed positive result for the ANA and other autoantibodies, shown on table 1. This was similar to the previous report of increased familial autoimmune responses. However there were no data of the HLA of our patients, due to lack of fund.

Systemic sclerosis seems to result from a multifactorial process. Many studies reporting familial aggregation have been published.[3,5] The implication of genetic factors is supported by other evidence, for example, the increased prevalence of autoimmune responses (ANA) and other autoimmune diseases in relatives of patients with SSc and a higher incidence of some genetic polymorphisms and HLA associations.

Table 1 Autoantibodies of two patients

Autoantibodies	Patient 1	Patient 2
ANA	14.32	14.55
Anti-nRNP/Sm	(-)	(+++)
Anti-Sm	(-)	(+)
Anti SS-A	(-)	(-)
Anti-Ro-52	(-)	(++)
Anti SS-B	(-)	(-)
Anti-Scl-70	(+++)	(-)
Anti-CENP B	(-)	(+++)
Anti ds-DNA	(-)	(-)
Anti-Rib.P-Protein	(-)	(-)

Clinical manifestation

Raynaud's phenomenon used to be described as initial complaint in approximately 70% of patients with SSc.[4] Both of our patients also have Raynaud's phenomenon as the initial complaint. Both of the patients were diagnosed to have diffuse type cutaneous SSc, base on the skin involvement. The mother had lung involvement which might be part of the manifestation of SSc. Further investigation such as high resolution CT scan should be done to evaluate the fibrosis in the lung, this will determine the prognosis and also the decision to treat more aggressively with the cytostatic agent (cyclophosphamid) for better outcome.[9] There are several reports of familial scleroderma, further research is needed to reveal possible genetic predisposition to the disease, especially in Asian Country.

SUMMARY

We have reported two cases of SSc in two generations: a mother and her offspring. Genetic and autoantibodies showed important role in the case of SSc.

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