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Progressive Systemic Sclerosis with Interstitial Lung Disease Post Radio Ablation in Graves Disease's Patient: A Case Report

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ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease marked by degenerative microvascular abnormalities and immune system activation, resulting in skin and internal organ fibrosis. The link between thyroid problems and systemic sclerosis is unknown. Although several studies have demonstrated that patients with systemic sclerosis develop Graves' illness as the condition progresses, only a few have reported that Graves' patients develop progressive systemic sclerosis. It is an uncommon instance of multiple autoimmune illnesses in which SSc develops gradually after the birth of the first child and the patient had Graves' disease since the age of 17 and had thyroid ablation 5 years ago. SSc illness has a characteristic clinical appearance, involving the skin to the rest of the body and internal organs, particularly the lungs.

1. Introduction

Systemic sclerosis is a multisystem autoimmune disease that affects small arteries, microvessels, and fibroblasts resulting in vascular obliteration, collagen accumulation, and fibrosis of the skin and internal organs.[1 2] Grave's disease is a systemic autoimmune disorder characterized by the infiltration of thyroid antigen- specific T cells into thyroid-stimulating hormone receptor (TSH-R) expressing tissues.[3] Progressive Systemic Sclerosis developed in a Grave's disease is rare. We reported a Grave's disease patient with progressive SSc.

2. Case Ilustration

A 32-year-old Indonesian woman has been diagnosed with Graves' illness since she was 17 years old. A 20-kilogram weight loss, fine tremors, and heat sensitivity were all revealed by the patient. Antithyroid medications and ablation with radioactive iodine (RAI) had been used to treat the patient.

After five years of treatment, her skin, face, and fingers on both hands tightened, and she developed dyspnea within a month. The patient married in January 2018 and had miscarried four months later. Later she got pregnant and had normal delivery in August 2019, and one month later, skin tightening began on both hands and quickly spread all over the body. When exposed to cold air, the patient feels discomfort in the extremities and turns blue. The patient then developed dyspnea, which worsened as

she walked.

The clinical examination revealed blood pressure of 110/70 mmHg, pulse rate of 96 beats per minute, breathing rate of 28 breaths per minute, and salt and pepper appearance on her skin. A louder P2 heart sound was discovered during chest examination; no rales or extra breath sounds were discovered. Raynaud's phenomenon and gangrene affected the fingers. There was no evidence of arthritis, tremors or edema.

Hemoglobin was 12 g/dL, leukocyte count 4980 mg/dL, erythrocyte sedimentation rate 45-67 mm/hour, ureum 19.8 mg/dL, serum creatinine 0.7 mg/dL, SGOT 18 mg/dL, and SGPT 14 mg/dL, according to the findings of the laboratory tests. The urine test revealed no protein and nor erythrocytes. The anti-TPO concentration was 6.64 IU/mL, while the TRAb concentration was 2.26 IU/mL.

The chest X-ray showed no abnormalities. Sinus tachycardia was detected on the ECG, and pulmonary hypertension was discovered on echocardiography. The superior lobe apico-posterior segment, most of the inferior lobe, and most of the left inferior lobe lung were all found to have ground-glass opacities on her chest CT scan.

The progression of SSc illness, which affected internal organs, was not accompanied by laboratory data. There were no positive results when the ANA specific for SSc was examined. The results of the ANA test using the immunofluorescence method revealed that the patient had positive ANA with a speckled pattern with titer of 1:10000. The laboratory tests were continued with a specific autoantibody profile for SSc utilizing a Euroimmun dipstick, which yielded negative results. (Figure 8)

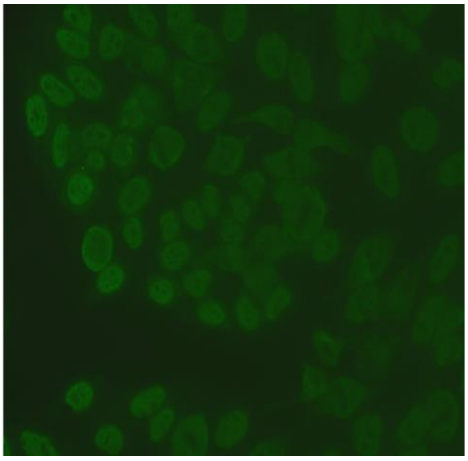


Figure 1. Speckled pattern

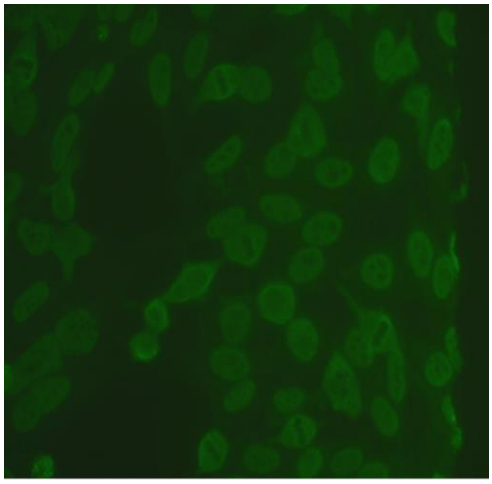


Figure 2. Speckled pattern

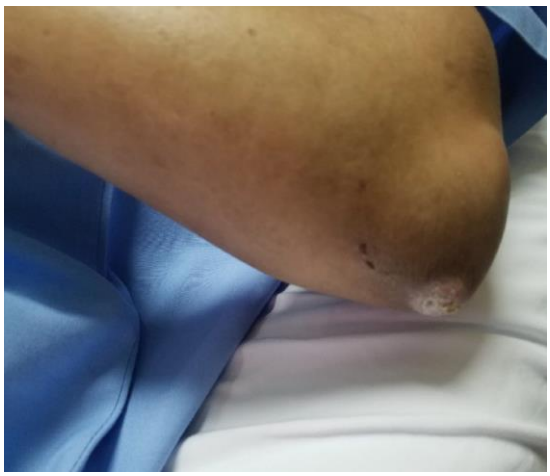


Figure 3. Image of fibrosis

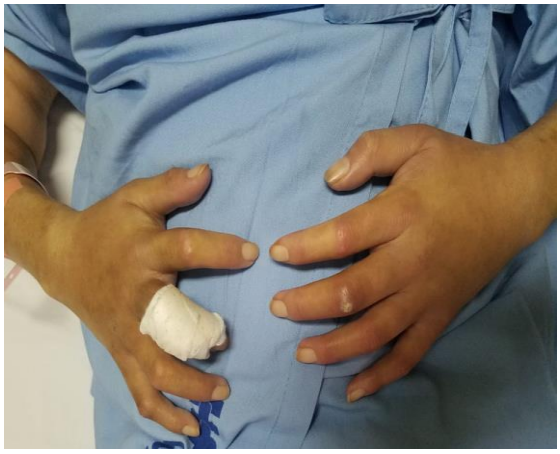


Figure 4. Fibrosis of the hand

Figure 5. Digital ulcer and gangrene of the fingers

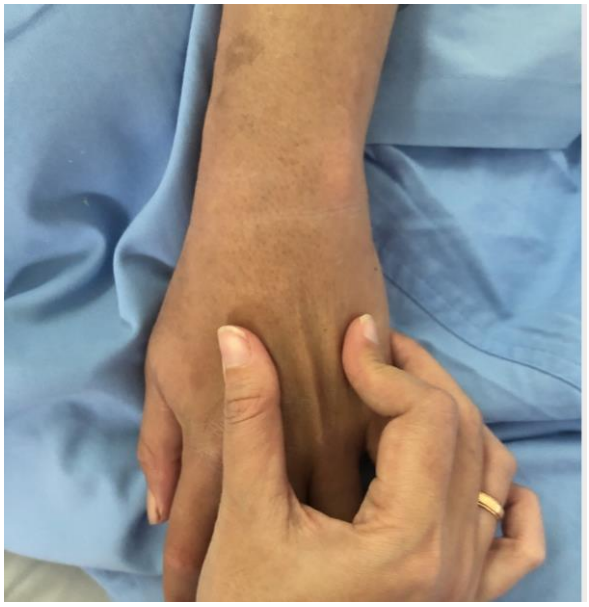
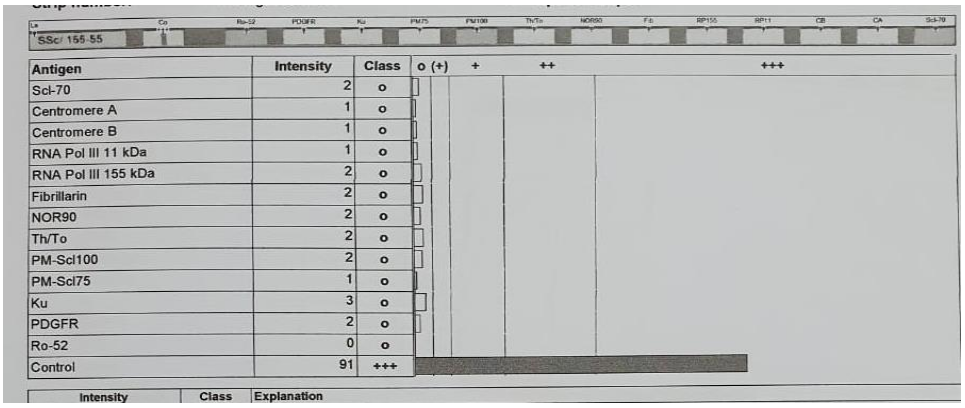
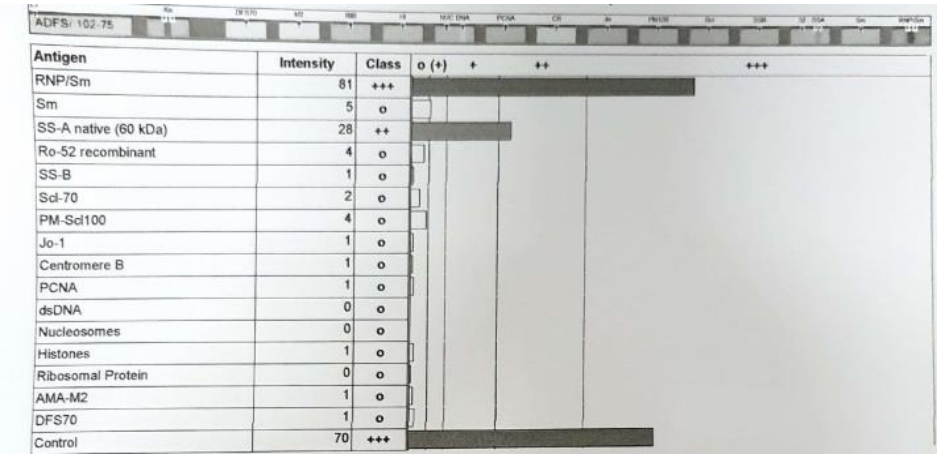


Figure 6: Skin fibrosis improved after the sixth cycles of cyclophosphamid treatment



Antigen	Intensity	Class
Scl-70	2	o
Centromere A	1	o
Centromere B	1	o
RNA Pol III 11 kDa	1	o
RNA Pol III 155 kDa	2	o
Fibrillarin	2	o
NOR90	2	o
Th/To	2	o
PM-Scl100	2	o
PM-Scl75	1	o
Ku	3	o
PDGFR	2	o
Ro-52	0	o
Control	91	+++

Figure 7. A specific autoantibody profile for SSc



Antigen	Intensity	Class
RNP/Sm	81	+++
Sm	5	o
SS-A native (60 kDa)	28	++
Ro-52 recombinant	4	o
SS-B	1	o
Scl-70	2	o
PM-Scl100	4	o
Jo-1	1	o
Centromere B	1	o
PCNA	1	o
dsDNA	0	o
Nucleosomes	0	o
Histones	1	o
Ribosomal Protein	0	o
AMA-M2	1	o
DFS70	1	o
Control	70	+++

Figure 8. Non Specific ANA Profile for SSc

Following the positive ANA immunofluorescence test and the negative autoantibody profile specific for SSc test in this patient, the ANA profile was examined for additional autoimmune disorders. As indicated above, the ANA profile findings were obtained.

Cyclophosphamide, sildenafil, diltiazem, and dexamethasone were used in the patient's treatment. The patient gained weight and her skin and dyspneu symptom improved after the six cycles of cyclophosphamid intravenous treatment.

The patient received six months of IV cyclophosphamide and then continued with mycophenolate mofetil (MMF). The patient's condition improved.

3. Discussion

SSc is a multisystem autoimmune disease that affects small arteries, microvessels, and fibroblasts resulting in vascular obliteration, collagen accumulation, and fibrosis of the skin and internal organs.[1 2]

In the literature, the link between SSc and thyroid disease has been discussed. Graves' disease has been discovered in SSc patients in few situations. Graves' disease was discovered in three of the 210 SSc patients. [4 5] However, Graves' illness following ablation and miscarriage that advances to SSc is extremely uncommon. After ablation, just one case of minimal cutaneous systemic sclerosis was reported and there have been no incidences of progressing disease in Graves' disease patients.[6]

Several pathways contribute to the etiology of SSc, including genetic differences, infection, and environmental variables that promote vascular damage, fibrosis, and immunological activation. Prior to fibrosis, vascular injury and immune activation are signs of vascular damage. Ischemia-reperfusion injury results in oxidative stress, which exacerbates vascular damage. Endothelial cells become activated and dysfunctional as a result of vascular damage, and their expression of vascular endothelial cell adhesion molecule-1 and endothelial leukocyte adhesion molecule-1 increases. [7]

One of the most significant aspects is genetics. BANK1, C8orf13-BLK, IL-23R, IRF5, STAT4, TBX21, and TNFS4 are just a few of the genes involved in the development of SSc. In severe cases, HLA-B8 was found, while DR2 and DR5 were found in mild cases. Drugs like Bleomycin, pentazocine, and cocaine are among the environmental factors that contribute to the development of SSc. Radiation therapy can produce de novo SSc and worsening of tissue fibrosis in SSc patients. Individuals with a genetic predisposition can be triggered by physical trauma.[7]

In 80 percent of SSc patients, vitamin D insufficiency has been identified. The intensity of skin involvement is related to vitamin D levels. Many infectious organisms (bacteria and viruses) have been hypothesized as potential triggering factors, however there is no direct link between infection and SSC. Parvovirus B19, human cytomegalovirus, hepatitis B virus, retrovirus, helicobacter pylori, and chlamydia are among the pathogens implicated. [7]

Thyroid ablation was used to treat the patient's autoimmune Graves' disease. After getting married, the patient's illness worsened, and she developed vasculitis and skin tightening after giving birth to her first child. The final diagnosis was progressive systemic sclerosis in a Graves' disease patient after a thorough investigation.

RAI was conducted on this patient, and the existence of pregnancy and miscarriage may have induced systemic sclerosis in this patient who already had genetic presdisposition. HLA testing should be performed to look for evidence of hereditary variables, however this patient has not been evaluated. Miscarriage and pregnancy are known to increase the risk of developing systemic sclerosis and aggravating autoimmune illness through microchimerism processes. TH1 and TH2 cytokines are stimulated by pregnancy. Through vascular damage, TH1 stimulates systemic sclerosis and causes endothelial activation and dysfunction as a result. [8 9]

According to a longitudinal investigation, there is a link between SSc and Graves' Disease. Graves' disease was discovered in the early stages of systemic sclerosis, according to some journals. [4] Graves' disease advanced in three cases, but only one case of systemic sclerosis progression in a patient with Graves' disease was documented.[6] This is assumed to be due to vitamin D insufficiency and TH1 immunological processes.[4,6,7]

Thyroid disease is also still debated in patients with systemic sclerosis, possibly because TH1 stimulates other TH1 reactivity in the body, stimulating other autoimmune in the body and, when combined with genetic and environmental factors, causing autoimmune phenomena in different organs in one subject. [5,7] It's also possible that this caused the systemic sclerosis in this Graves' disease patient.

This patient can be diagnosed with systemic sclerosis based on the **ACR/EULAR Revised Systemic Sclerosis Classification Criteria**, with a score of > 9, although antibodies that are often seen in systemic sclerosis were not found in this case. Anti-topoisomerase I, anticentromere, and anti-RNA polymerase III autoantibodies have been found in patients with systemic sclerosis based on the **ACR/EULAR Criteria**, but they are still in development.[10] Currently, several new antibodies related to systemic sclerosis have been discovered, and it can even be found before the diagnosis is made, as SSA and anti-RNP autoantibodies were found in this patient.[2]

Ro/SSA has a sensitivity of 42 percent and was found to be 15-19 percent in SSc patients, whereas anti-U1-RNP was found to be 4.8-4.9 percent in patients with systemic sclerosis, according to recent literature. Anti-RNP is linked to the development of Pulmonary Artery Hypertension (PAH), which is consistent with the clinical course of this patient with PH and ILD.[11]

4. Conclusion

Patients with recognized autoimmune illnesses should be closely watched for the emergence of new autoimmune problems. As a result, patients can be tested for HLA and autoantibodies early on, allowing for the early detection of additional autoimmune disorders and the improvement of patient lives and general quality of life.

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