A Woman with Systemic Sclerosis, Sjogren's Syndrome, and Chronic Limb Ischemic Fontaine IV Digiti II Pedis Sinistra

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ABSTRACT
Systemic sclerosis is a systemic disease affecting the skin connective tissue, internal organs, and blood vessel walls, characterized by endhotel dysfunction, fibrosis, and autoantibody production. Sjogren's syndrome can appear as part of other autoimmune diseases, including systemic sclerosis (11-24%). Chronic limb ischemia is a type of peripheral arterial disease where there is blockage of the peripheral arteries due to an inflammatory or atherosclerosis process that causes arterial stenosis or thrombus formation. The Fontaine classification can assess the severity degree. A 48-year-old woman presents with stiff skin almost all over the body, especially the face, hands, feet, and back skin. She also complained of blackened and numb toes. Physical examination revealed positive Raynaud's phenomenon, Pitting scare, and deformity of both fingers. The systemic sclerosis diagnostic score was 18, which means the patient was positive for systemic sclerosis. ANA test showed strong positive Anti La / SS-B and Ro-60, which supports Sjogren's syndrome. In Fontaine classification, patients are assigned to Fontaine IV digiti II pedis sinistra. She received immunosuppressants, corticosteroids, antiplatelet agents, statin, and performed angiography. Autoimmune diseases can attack multiple organs and rarely stand on their own. Comprehensive management can provide better clinical results.

Keywords: *Systemic sclerosis, Sjogren's syndrome, Chronic limb ischemia*

1. INTRODUCTION

Systemic sclerosis is a systemic disease affecting the skin connective tissue, internal organs, and blood vessel walls, characterized by endothelial dysfunction, fibrosis, and autoantibodies production. At the same time, Sjogren's syndrome found in this case can also appear as part of other autoimmune diseases, including systemic sclerosis. Appropriate therapeutic management is needed to prevent more severe complications.

2. CASE

A 48 years old woman presented with the chief complaint of skin stiffness about eight months ago: at first , stiffness was only felt in the legs then spread to the hands, body, and almost the whole body. She also complained of fingers and toes become difficult to move. The patient also complained of purplish toes when exposed to cold water since eight months ago. The second finger of the left foot has been looking red since three months ago, and it has started to look black one month ago and now is numb. The patient also complained of thinning hair due to hair loss since eight months ago. The patient had checked himself at the hospital in his area but did not experience any changes. Physical examination revealed Raynaud's phenomenon was positive, pitting scares in the fingers, deformities in both hands fingers, skin stiffness all over the body so that the fingers were difficult to move.

Table 1. Laboratory Result Data

	Result	Normal result	
Hb	11,	12-15.6	g/dl
Hct	33	33-45	%
Leukocyte	**12,**	4.5-11.0	x 10^3/uL
Erithrocyte	**3,7**	4.10-5.10	x 10^6/uL
Thrombocyte	28	150-450	x 10^3/uL

Erithrocyte Index			
MCV	88,1	80.0 – 96.0	/um
MCH	29,8	28.0 – 33.0	Pg
MCHC	33,8	33.0 – 36.0	g/dl
RDW	15,4	11.6 – 14.6	%
MPV	8,2	7.2 – 11.1	Fl
PDW	**16**	25 – 65	%

Type count			
Eosinophils	0,70	0.00 – 4.00	%
Basophils	0,60	0.00 – 2.00	%
Netrophils	**80,70**	55.00 – 80.00	%
Limphocyte	**12,40**	22.00 – 44.00	%
Monocyte	5,60	0.00 – 7.00	%

Hemostasis			
PT	**19,5**	10,0 – 15,0	Detik
aPTT	35,2	20,0 – 40,0	Detik
INR	1.490		

GDS	102	60-140	mg/dl
SGOT	**85**	<31	g/dl
SGPT	**195**	<34	mg/dl
Creatinin	**0,7**	0.7-1.3	mg/dl
Ureum	**14**	<50	mg/dl
Albumin	**2,4**	3,5-5,2	g/dl
HbsAg	**Non Reactive**	Non Reactive	-
Sars-Cov2	**Non Reactive**	Non Reactive	

Electrolyte			
Natrium	139	136-146	mmol/L
Kalium	**2,4**	3.3-5.1	mmol/L
Calcium	**1,12**	1,17-1,29	mmol/L

Hepatitis Serology
Total anti-Hbc : Negative
Total anti-HCV : Negative
ANA Cytobeads Results **Support existence of Primary Sjogren's Syndrome and Progressive Systemic Sclerosis (PSS)**

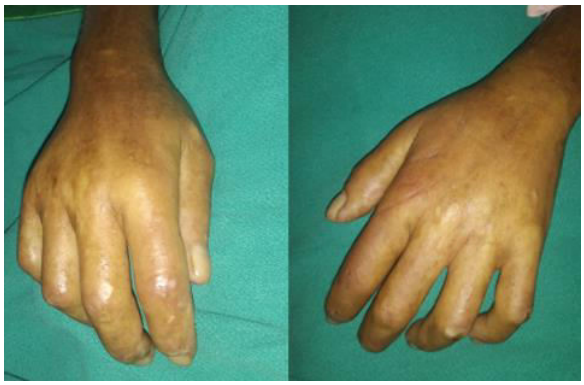

Figure 1. Pitting scar on the right and left fingers

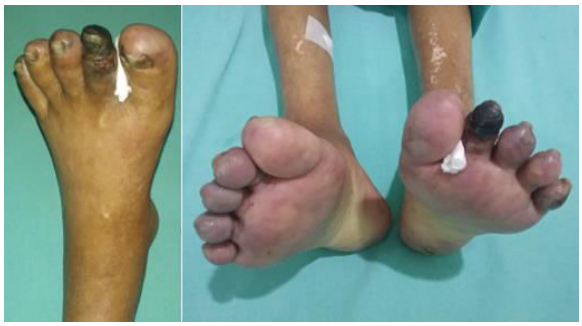

Figure 2. Chronic Limb Ischemic on digiti II pedis sinistra (left). Raynaud's phenomenon (right)

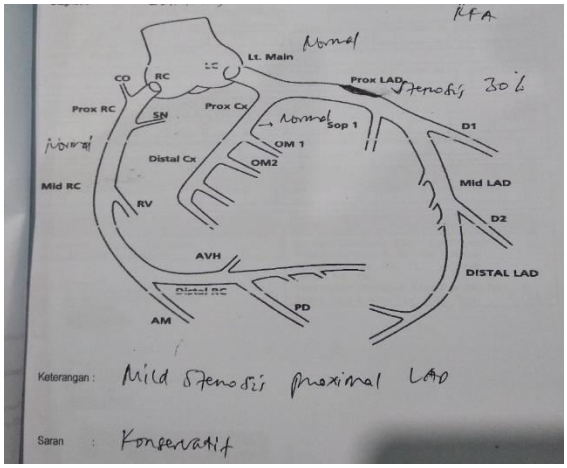

Figure 3. Digital Subtraction Angiography results

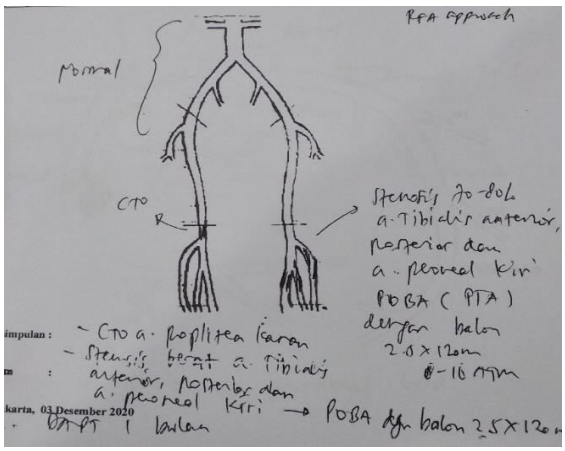

Figure 4. Percutaneous Transluminal Angioplasty results

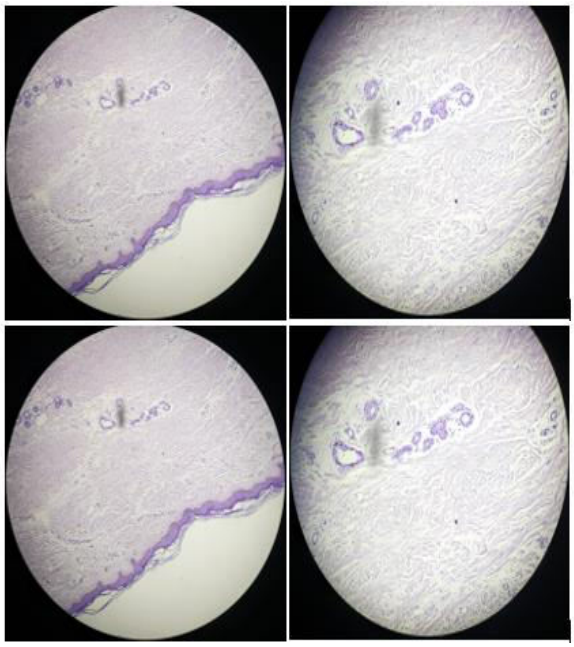

Figure 5. Skin biopsy results

Dilusi	1/100
Pola sel HEp-2	Nuclear fined speckled chromatin negatif ; cytoplasmic fined speckled chromatin negative; intensitas +4

	Kompartemen 1		Kompartemen 2		Kompartemen 3		Kompartemen 4	
Marker	La/SS-B	Jo-1	Sm	RNP-Sm	dsDNA	Scl-70	Ro-60	Ro-52
Hasil	Positif kuat	Negatif	Negatif	Negatif	Negatif	Positif kuat	Positif kuat	Negatif

Hasil Positif	Relevansi Klinis
La/SS-B	Sering dijumpai pada *Sjorgen Syndrome* Primer
Jo-1	Dijumpai pada Polimiositis, Dermatomiositis
Sm	Dijumpai pada *Systemic Lupus Erythematosus* (SLE)
RNP-Sm	Pada titer yang tinggi, spesifik untuk *mixed connective tissue disease* (MCTD) bersama dengan ANA pada kondisi *rheumatoid arthritis* (RA), SLE, dan PSS
dsDNA	Dijumpai pada *Systemic Lupus Erythematosus* (SLE)
Scl-70	Dijumpai pada *Progressive System Sclerosis* (PSS)
Ro-60	Sering dijumpai pada *Sjorgen Syndrome* Primer, Neonatal Lupus
Ro-52	Sering dijumpai pada *Sjorgen Syndrome* Primer, Neonatal Lupus

Nilai Rujukan :

ANA	Dilusi
Negatif	< 1/80
Positif	>= 1/80

Interpretasi Hasil	Berdasarkan hasil pola sel HEp2 (Nuclear fined speckled chromatin negatif ; cytoplasmic fined speckled chromatin negative; intensitas +4), dan positif (kuat) pada antigen La/SS-B, Scl-70, Ro-60, dan negatif pada kelima antigen. Hasil cytobeads ANA: mendukung adanya Sjorgen Syndrom Primer, dan Progressive Systemic Sclerosis (PSS).

Figure 6. ANA cytobeads results

From the laboratory test results (Table 1), we found leukocytosis, lymphocytopenia, decreased erythrocyte, albumin, natrium, kalium, and calsium, and increased PT, SGOT, and SGPT. Cytobeads ANA results supported the existence of Primary Sjogren's Syndrome and Progressive Systemic Sclerosis (PSS). From digital subtraction angiography and percutaneous transluminal angioplasty (Figure 3, 4), we found chronic total occlusion artery popliteal dextra and severe stenosis artery tibialis anterior sinistra. The skin biopsy results supported Scleroderma diagnosis (Figure 5).

3. DISCUSSION

From anamnesis, physical examination, and supporting examination, the patient's diagnosis suggests Systemic sclerosis, Sjogren's syndrome, and Chronic limb ischemic Fontaine IV digiti II pedis sinistra. Systemic sclerosis is a systemic disease affecting the skin connective tissue, internal organs, and blood vessel walls, which is characterized by

endothelial dysfunction, fibrosis, and the production of autoantibodies.

Table 2. The American College of Rheumatology/European League Against Rheumatism (EULAR) criteria for the classification of systemic sclerosis[1]

Item	Sub-item(s)	Weight /score
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anti centromere Anti–topoisomerase I Anti–RNA polymerase III	3
* These criteria apply to any patient considered for inclusion in an SSc study. The criteria do not apply to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).		
The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of _ nine are classified as having Systemic definite sclerosis.		

Table 3. Criteria of classification of diffuse and limited cutaneous systemic sclerosis according to LeRoy et al. [2]

Diffuse cutaneous SSc (dcSSc) The onset of Raynaud's phenomenon within one year of onset skin changes(puffy or hidebound) Truncal and acral skin involvement Presence of tendon friction rubs Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement Absence of ACA Nail fold capillary dilatation and capillary destruction Antitopoisomerase antibodies (30% of patients)
Limited cutaneous SSc (lcSSc) Raynaud's phenomenon for years (occasionally decades) Skin involvement limited to hands, face, feet, and forearms (acral) or absent A significant late incidence of pulmonary hypertension, with or without interstitial lung disease, trigeminal neuralgia, skin calcifications, and telangiectasia A high incidence of ACA (70–80%) Dilated nail fold capillary loops, usually without capillary dropout

The ANA test showed a strong positive result at Scl-70 (Figure 6). Based on the diagnostic criteria (Table 2), after the components present in the patient are included, this patient has a total score of 18. With this total score, the patient can be classified into systemic sclerosis diffuse type (Table 3).

Optimal management of SSc is still a challenge today. The principle of therapy in SSc is the improvement of the general condition by paying attention to the factors of nutrition, hygiene, and psychological support. Treatment of the symptoms experienced by the patient. Furthermore, therapy is aimed at three pathogenesis, vasculopathy, fibrosis, and immunologic disorders (inflammation, immunomodulation, and autoimmunity). SSc is incurable but treatable, although the response is slow.[2]

Table 4. 2016 American College of Rheumatology/European League Against Rheumatism/ (ACR/EULAR) Criteria for Primary Sjögren Syndrome[3]

Criteria	Score
Salivary glands with focal lymphocytic sialadenitis and focus score 1 foci/4 mm^2	3
Positive anti-SSA antibodies	3
Ocular staining score 5 (or van Bijsterveld 4) in at least one eye	1
Schirmer test 5 mm/5 min in at least one eye	1
Unstimulated whole saliva 0.1 ml/min	1
Included in the criteria for Primary Sjögren Syndrome if the total score ≥ 4	

ANA examination resulted in strongly positive Anti-La/SS-B and Ro-60. These results are often found in Sjogren's

syndrome. From EULAR criteria for Primary Sjogrens Syndrome (Table 4), the patient's score is four which is included in the criteria for Primary Sjogrens Syndrome.

Primary Sjogren Syndrome is an autoimmune disease that is mainly characterized by eyes and mouth dryness. Various manifestations involving the skin, neurology, hematology, respiratory, gastrointestinal, genitourinary, and musculoskeletal systems can complicate the clinical course.[4]

Therapy for systemic sclerosis and Sjogren's syndrome in this patient includes the administration of vasodilators (nifedipine 1x10 mg), ACE inhibitor agents (ramipril 1x5mg), omeprazole 2x20mg, immunosuppressants (azathioprine 1x50 mg), methotrexate 10mg/week and methylprednisolone 2x8mg. Artificial tears eye drops are also given as supportive therapy in Sjogren's syndrome. Supporting nutrients such as folic acid 1x800mcg and Vitamin D3 3x1000IU are also given as immune nutrients in this patient. The therapeutic goals are to relieve symptoms, prevent complications of the disease (especially in the eyes and mouth) and treat serious and/or life-threatening systemic manifestations with immunosuppressive therapy. Systemic disease is a major prognostic determinant of systemic sclerosis and is associated with autoimmune-mediated organ dysfunction that can eventually become irreversible. The use of systemic therapy (glucocorticoids, antimalarials, immunosuppressive agents, intravenous immunoglobulins, and biologic agents) should be limited to patients with active systemic disease. The choice of therapy depends on the severity of the symptoms, the severity of the disease, and the involvement of internal organs. Synthetic immunosuppressive agents should be used as steroid-sparing agents, without evidence to support the choice of one agent over another. In musculoskeletal involvement, leflunomide, sulfasalazine, and azathioprine are considered to have the same efficacy as steroid-sparing agents, except in situations with evidence of other major organ involvement (e.g., interstitial lung disease) where azathioprine is preferred for treating multi-system disease. The patient was given azathioprine therapy with an initial dose of 50 mg/24 hours. Then the dose was increased to 100 mg/24 hours.[5]

In addition to the two diagnoses above, the patient was also diagnosed with chronic limb ischemia. Chronic limb ischemia is one type of peripheral arterial disease, or it can also be called peripheral arterial occlusive disease, which is a blockage in the peripheral arteries due to atherosclerosis or an inflammatory process that causes narrowing the lumen of the arteries (stenosis), or thrombus formation, causes an increase in vascular resistance which can lead to a decrease in perfusion pressure to the distal area. Studies show that chronic atherosclerotic conditions of the extremities produce stenotic lesions. The hemodynamic mechanisms and processes that occur in chronic limb ischemia are very similar to those in coronary artery disease. The most common site for chronic limb ischemia is in the lower limbs and is rarely found on the fingers.[6] The main symptom is a pain in the area where the blood vessels are narrowed. If the affected blood vessels are leg veins, then the initial signs and symptoms are pain (claudication) and a feeling of fatigue in the affected muscles. Because this disease generally occurs in the feet, the sensation is felt when walking and may disappear at rest. As the disease worsens, symptoms may occur during light physical activity, even at any time, even at rest.[7] The severity can be assessed by the Fontaine classification as shown in the table below :

Table 5. Fontaine Classification[8]

Fontaine Classification	
Stage	Symptoms
I	Asymptomatic
II	Intermittent claudicatio
III	Ischemic pain at rest
IV	**Ulceration or Gangrene**

Based on the table above, the patient was diagnosed with Chronic Limb Ischemia Fontaine IV. The patient was given Clopidogrel 75 mg/24 hours, Aspilet 80 mg/24 hours, Atorvastatin 40 mg/24 hours, and angiography was performed. After that, it is known that there is a total blockage in arteria poplitea dextra and blockage 70-80% in arteria left tibialis anterior. On arteria peroneus sinistra performed Percutaneous Occlusion Baloon Angioplasty.

The goals of treatment are to reduce clinical symptoms such as claudication, improve quality of life, prevent complications, heart disease, stroke, and amputation. Treatment is based on clinical symptoms found in risk factors and the results of clinical and supporting examinations. There are three main approaches to treating chronic limb ischemia, lifestyle changes, pharmacological therapy, and, if necessary, surgical intervention.[7]

4. CONCLUSION

Autoimmune diseases can attack multiple organs and rarely stand alone. Comprehensive management can provide better clinical outcomes and good quality of life for patients. Immunonutrition plays an essential role in the management of an autoimmune disease. A continuous and comprehensive evaluation is needed on its management and the possible complications that can arise.

5. CONFLICT OF INTEREST

The author reported no potential conflict of interest.

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