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Pulmonary Hypertension in Systemic Lupus Erythematosus with Raynaud's Phenomenon: Case Report

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs such as skin, joints, kidneys, heart, lungs, nervous system and blood. Pulmonary hypertension is a rare complication of SLE.¹ Systemic lupus erythematosus associated with pulmonary hypertension was defined as an increase in the average pressure in the pulmonary artery at rest ≥ 25 mmHg with pulmonary capillary wedge pressure ≤ 15 mm Hg and an increase in pulmonary vascular resistance.² The prevalence of pulmonary hypertension in SLE approximately 0.5 to 17.5%. Predictors factors of the occurrence of pulmonary hypertension in LES is Raynaud's phenomenon, anti-U1RNP antibody, and antibody positive anticardiolipin.³ A woman aged 37 years came with a chief complaint of pain in the fingers and toes with black-colored wounds felt since 6 months before admission. From the anamnesis, physical examination, support to meet 5 of the classification criteria for systemic lupus erythematosus based on the 1997 ACR criteria which includes manifestations of arthritis, mucocutaneous, serositis, lupus anticoagulant, and ANA IF positive. In these patients also found the typical signs and symptoms of Raynaud's phenomenon which leads to the symptoms of pain in the fingers of both hands when exposed to cold and pale to red when heated and has been confirmed from the results of arteriography. From the results of echocardiography reveal any pulmonary hypertension. This patient was treated with steroids, immunosuppressants and antiplatelet. The case was removed because of pulmonary hypertension is a complication LES rare and necessary sharpness in diagnosis. Patients with pulmonary hypertension of unknown or untreated can become a progressive right heart failure and lead to death.³

1. Introduction

Lupus erythematosus is an autoimmune disease that involves various organs of the body including the pulmonary system. Pulmonary hypertension is one of the rare complications of SLE.⁴ The prevalence of definition of pulmonary hypertension, and different diagnostic approaches (echocardiography versus

pulmonary hypertension in SLE is about 0.5-17.5%. Estimates of the prevalence of pulmonary hypertension in SLE vary, due to multiple factors such as varying populations, lack of common right heart catheterization).³ Lupus erythematosus is the second leading cause of pulmonary hypertension

after systemic sclerosis-related connective tissue disease. Secondary Raynaud's phenomenon often manifests in patients with connective tissue diseases such as systemic sclerosis, SLE, antiphospholipid syndrome, cryoglobulinemia and other vasculitis. It has been found that Raynaud's phenomenon occurs in about 10-45% of SLE patients.⁵

Pulmonary hypertension is a predictor of survival in SLE patients. The coexistence of Raynaud's phenomenon is associated with a good prognosis in SLE patients with pulmonary hypertension. The role of immunosuppressant therapy in LES-PH is controversial. Some case reports reported improvement with immunosuppressant therapy, but several other case reports showed clinical deterioration.

In this article, we discuss a case of pulmonary hypertension in a patient with systemic lupus erythematosus with Raynaud's phenomenon, a 37-year-old woman diagnosed with systemic lupus erythematosus.

2. Case Illustration

A 37-year-old female patient complained of intermittent joint pain for 1 year, hair loss, and fatigue. Six months earlier the patient complained of pain in the fingers of both hands when exposed to cold and pale in color and then became reddish when warmed. The patient complained of small wounds on his hands and feet since the last 4 months which initially had pus, then dried and blackened skin, sometimes pain, frequent mouth ulcers, weight loss

of 12 kg in 6 months, joint pain and difficulty walking due to weakness. Os checked to the hospital and said systemic lupus erythematosus was treated with methylprednisolone 1x16 mg, and digoxin 1x0.25 mg, furosemide 1x40 mg, spironolactone 1x50 mg, but the complaints did not improve.

On the day of hospital admission, the patient was referred to Dr Sardjito Hospital, with the main complaints of weakness, pain in the fingers and toes accompanied by small dry and black wounds, canker sores, hair loss, decreased appetite, joint pain, and difficulty walking. He denied fever, cough, shortness of breath, rash on the skin, hardened skin, nausea and vomiting, normal bowel and bladder. The patient works as a farmer, has 2 children, the first child is 16 years old, the second child is 14 years old, there is no history of miscarriage, hypertension and diabetes mellitus is denied.

From the results of the physical examination, the general condition was weak, *compos mentis* consciousness, blood pressure 100/70 mmHg, pulse 98 times/minute, respiratory rate 20 times/minute, temperature 36.5°C, oxygen saturation 97%, weight 37 kg, TB 158 cm, and BMI 14.8. The results of head and neck examination were within normal limits, the heart had cardiomegaly, there was no abnormality in the abdomen, multiple blackened dry ulcers were seen in the bilateral manus et tarsal region, cold acral, and tenderness. The pulses of all four extremities were normal and peripheral saturation was not measured in both lower extremities, digits II-V of the right and IV digits of the left manus.

Figure 1. The four extremities appear to have multiple black ulcers

On blood examination, the result is hemoglobin 13.6 g/dL, leukocytes $9.24 \times 10^3/\mu\text{L}$, platelets $150 \times 10^3/\mu\text{L}$, segment 89.5%, lymphocytes 8, 2%, albumin 3.66, SGOT 54, SGPT 89, GDS 114 mg/dL, BUN 18.1, creatinine 0.54, sodium 144, potassium 3.44, PPT (control) 15.8 (13.4), APTT (control) 29.1 (30.4), INR 1.17, fibrinogen 236, D-dimer 998. Urinalysis results showed +2 proteinuria and no cylinder/cast, positive ANA IF, ACA IgG marker 5.7 (normal <10), ACA IgM 2,3 (normal <7), 2-GLP1 IgM 1.5 (normal <5), 2-GLP1 IgG 8.4

(normal <5), patient LA1 126.6 (normal 31-44), control LA1 40.6, confirm LA2 51.9 (normal 30-38), control LA2 38.2, ratio (LA1:LA2) 2.44 ($N < 1.2$, positive severe > 2 , 0), conclusion: LA positive severe. Electrocardiography results showed sinus rhythm, heart rate 96 beats/minute, left axis deviation (LAD), left atrial enlargement (LAE), and left ventricular hypertrophy (LVH). On chest X-ray examination, there were no abnormalities and there was cardiomegaly.

Figure 2. Chest X-ray

On arterial Doppler ultrasound: bilateral superior extremity arterial system abnormalities were not seen, waves end diastolic of the distal anterior tibial artery, distal posterior tibial arteries, bilateral dorsalis pedis arteries suggest

mild stenosis of these arteries, suggest arteriography. Then an arteriography examination was performed with the results obtained to obtain a picture that supports Raynaud's Phenomenon (secondary).

Figure 3. Arteriography

Echocardiography results showed RV dilatation, decreased LV global systolic function with an EF of 18%, grade I diastolic dysfunction, decreased RV systolic function, global hypokinetics, moderate MR, moderate TR, moderate PR, mild AR, mild pericardial effusion, and high probability pulmonary hypertension, mPAP 37.6 mmHg.

The patient was diagnosed as systemic lupus erythematosus with manifestations of serositis, mucocutaneous and arthritis, Raynaud's Phenomenon with multiple ulcers, pericardial effusion mild, antiphospholipid syndrome, high probability pulmonary hypertension, and congestive heart failure chf III et causa cardiomyopathy. The patient was given ceftriaxone injection therapy 1 gr/12 hours, methylprednisolone 1x16 mg, myfortic 2x180 mg, aspirin 1x80 mg, amlodipine 1x5 mg, cilostazol 2x50 mg, nitrokat 2x5 mg, and paracetamol 3x500 mg.

3. Discussion

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects several organs such as the skin, joints, kidneys, heart, lungs, nervous system and blood. Pulmonary hypertension is one of the rare serious complications of SLE.⁴ The prevalence of pulmonary hypertension in SLE is about 0.5-17.5%. The predictors of pulmonary hypertension in SLE were Raynaud's phenomenon, positive anti-ribonucleoprotein antibodies, and positive anticardiolipin antibodies. The majority of patients with pulmonary hypertension in SLE were women (95%), young people aged 18-40 years, and 14% of SLE patients with pulmonary hypertension had Raynaud's phenomenon.³

Pulmonary hypertension is a progressive disease classified into primary and secondary, and is characterized by an increase in mean pulmonary artery pressure to more than 25 mmHg at rest and more than 30 mmHg during exercise, with a *mean pulmonary capillary wedge pressure* and *end-diastolic pressure*. left ventricular ≤ 15 mm Hg. Pulmonary

hypertension can increase morbidity and mortality, both primary and secondary forms associated with other conditions such as connective tissue disease or HIV.²

In patients suspected of having pulmonary hypertension, Doppler echocardiography is recommended to detect pulmonary hypertension, evaluate ventricular systolic and diastolic dysfunction, left ventricular enlargement or valvular heart disease. This method is non-invasive and can be used in patients with positive anticardiolipin antibodies or the antiphospholipid syndrome for early detection of right ventricular diastolic dysfunction. In this case, the diagnosis of pulmonary hypertension was known from the results of echocardiography that had been carried out with a result of mPAP37.6 mmHg. Right heart catheterization is required to confirm the presence of pulmonary hypertension and its severity, and to establish a specific diagnosis.⁶

Patients with unknown or untreated pulmonary hypertension can progress to dilated right heart failure and can lead to death. Several intensive immunosuppressant and vasodilator therapies have shown promising results in pulmonary hypertension associated with SLE.³ The role of immunosuppressant therapy in LES-PH is controversial. Some case reports reported improvement with immunosuppressant therapy, but several other case reports showed clinical deterioration. This result contrasts with pulmonary hypertension in systemic sclerosis which is generally ineffective with immunosuppressant therapy and often requires escalation of certain therapies.⁶

Raynaud's phenomenon is a functional disorder characterized by recurrent reversible vasospasm of the fingers and toes and often triggered by exposure to cold and stress, can be classified into primary and secondary based on the presence or absence of previously known associated diseases. Secondary Raynaud's phenomenon often manifests in patients with connective tissue diseases such as systemic sclerosis, SLE, antiphospholipid syndrome, cryoglobulinemia and other vasculitis. It has been found that Raynaud's phenomenon occurs in about

10-45% of SLE patients.⁵ In this case there are complaints of pain in the fingers of both hands when exposed to cold and pale, and then becomes red when warmed, which leads to the signs and symptoms of Raynaud's phenomenon. Raynaud's phenomenon in this case based on the results of the arteriography performed is secondary, most likely related to the systemic lupus erythematosus experienced.

In SLE with Raynaud's phenomenon, arthralgia, arthritis, and myalgia are not related to treatment modality or duration of disease. The mechanism of Raynaud's phenomenon in SLE is pulmonary arterial vasospasm due to endothelial dysfunction and an increased concentration of potent vasoconstrictors. The observation that Raynaud's phenomenon is associated with (PASP) *pulmonary artery systolic pressure*) can be explained in some patients who experience recurrent episodes of transient spasm of the pulmonary circulation in the lungs and hypoxia, leading to irreversible vascular structural changes, which in turn increase the pressure progressively resulting in increased pressure. to persistent pulmonary hypertension.⁷

Several pathological mechanisms are associated with SLE, including vasoconstriction, vasculitis, thrombosis, and anticardiolipin antibodies. Pulmonary arterial and arteriolar microangiopathy is critical for the immunopathogenesis of pulmonary hypertension in SLE. The presence of antiphospholipid antibodies and anti-endothelial cell antibodies and inflammation are part of the mechanisms that contribute to the development and progression of the proliferative lesions of this disease. Magadmi *et al.* Stating that patients with SLE and particularly women have systemic endothelial dysfunction. In addition, Raynaud's phenomenon has a generalized vasospastic tendency affecting multiple organs with endothelial dysfunction and altered vasoreactivity as possible mechanisms.^{8,9}

Systemic lupus erythematosus with secondary pulmonary hypertension and Raynaud's phenomenon tends to have high pulmonary arterial partial pressures at diagnosis, suggesting that Raynaud's phenomenon may be a marker of severity

of secondary pulmonary hypertension. Nonetheless, the association between Raynaud's phenomenon and pulmonary hypertension supports the possibility that pulmonary arterial vasospasm is involved in the pathogenesis of pulmonary hypertension.⁵ SLE patients with pulmonary hypertension tend to have a high disease activity index. Extrapulmonary symptoms of Raynaud's phenomenon are one of the main predictors of pulmonary hypertension in SLE, occurring in 75% of SLE patients with pulmonary hypertension and 10-45% of all SLE patients. Pleural effusion is rare in pulmonary hypertension.^{9,10}

High prevalence of antiphospholipid antibodies in SLE patients with pulmonary hypertension, which was found in 83% of patients with SLE and pulmonary hypertension, in 30-50% of SLE patients without pulmonary hypertension, compared to 7% in patients with systemic sclerosis. Pathogenesis aPL activates endothelial cells, monocytes, and platelets thereby triggering a prothrombotic state. Patients with these antibodies are more prone to develop thrombotic arteriopathies and therefore need to be aware of the development of chronic thromboembolic pulmonary hypertension. Elevated circulating levels of endothelin-1 have been reported in patients with aPL which may contribute to vasoconstriction and pulmonary hypertension.¹¹

SLE patients with pulmonary hypertension are generally treated with oxygen, anticoagulants, *calcium channel blockers* and vasodilators. However, there is no therapeutic regimen that is highly effective in treating SLE with pulmonary hypertension. The vasodilators used are selective and non-selective endothelin receptor antagonists, phosphodiesterase-5-inhibitors (PDE-5-I), and oral, inhaled, subcutaneous or intravenous prostanoids. Systemic lupus erythematosus with pulmonary hypertension results in persistent pulmonary vasoconstriction and leads to obliteration of the lumen of the small and medium pulmonary arteries due to plexiform lesion formation and thrombosis in situ. In addition, inflammatory components and immune dysregulation also play an important role in the pathogenesis of pulmonary hypertension in SLE and

therefore need to be treated with anti-inflammatory (steroids) and immunosuppressants. In this case the patient was treated with steroids, immunosuppressants and vasodilators.¹²

The relationship between intensive immunosuppressant therapy and improved survival is unclear.¹² However, patients should be treated aggressively with immunosuppressants and anti-inflammatories, in combination with vasodilators because the disease can be progressive. In certain cases, a combination of intensive immunosuppressants and vasodilators may be used.

Diagnosis of SLE often precedes the diagnosis of pulmonary hypertension, with a median time of 4.9 years. Several studies have estimated a poor prognosis with a survival of 13 months. Based on a systematic review, it was shown that several clinical factors were associated with survival, such as the magnitude of the pulmonary arterial pressure, thrombosis, thrombocytopenia, the presence of anti-cardiolipin antibodies, being pregnant, infection, Raynaud's phenomenon, plexiform lesions and pulmonary vasculitis. Pulmonary hypertension patients in SLE have a better prognosis than pulmonary hypertension patients in systemic sclerosis, where 3-year survival is about 75% in SLE patients compared to 47% in systemic sclerosis patients.⁶ Patients with anti-U1-RNP antibodies, anticardiolipin antibodies, and Raynaud's phenomenon should be seriously considered for screening, because there is a strong correlation between these predictors and the incidence of pulmonary hypertension.^{9,10}

4. Conclusion

Pulmonary hypertension is a rare complication of lupus erythematosus, occurring within the first 5 years of the onset of SLE diagnosis in most cases. Doppler echocardiography is recommended for early detection of pulmonary hypertension in SLE. Anti-U1-RNP, anticardiolipin antibodies, and Raynaud's phenomenon are predictors of pulmonary hypertension in SLE patients. Patients with unknown or untreated pulmonary hypertension can progress to

dilated right heart failure and can lead to death. Although no therapeutic regimen is highly effective in treating SLE with pulmonary hypertension, patients should be treated aggressively with immunosuppressants and anti-inflammatories, in combination with vasodilators because the disease can be progressive. The overall 5-year life expectancy of SLE patients with pulmonary hypertension is relatively good, about 83.9%. Pulmonary hypertension is a predictor of survival in SLE patients.

5. References

1. Eric F, Mosca M. Treat to target, remission and low disease activity in SLE. *Best Practice Res Clinic Rheumatology*. 2017. 31(3): 342-350.
2. Tselios K, Gladman D, Urowitz MB. Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management Strategies. *Open Access Rheumatology: Research and Reviews* 2017;9 1-9
3. Dhala A. Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus: Current Status and Future Direction. Hindawi Publishing Corporation *Clinical and Developmental Immunology*. Volume 2012, Article ID 854941, 12 pages
4. Hachulla E, Jais X, Cinquetti G. Pulmonary arterial hypertension associated with systemic lupus: results from the French Pulmonary Hypertension Registry. *CHEST Journal*. 2017. S0012-3692(17)31430-7
5. Kasparian A, Floros A, Gialafos E, Kanakis M, Tassiopoulos S, Kafasi N, Vaiopoulos G. Raynaud's phenomenon is correlated with elevated systolic pulmonary arterial pressure in patients with systemic lupus erythematosus. *SAGE Publications Los Angeles. Lupus* (2007) 16, 505-508
6. Johnson SR, Granton JT Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus. *Eur Respir Rev* 2011; 20:122, 277-286

7. Pérez-Peñate G. M, Rúa-Figueroa I, Juliá-Serdá G, *et al.* Prevalence and Predictors of Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus: The Journal of Rheumatology 2016; 43:2
8. Schreiber BE, Connolly M. J, Coghlan JG Pulmonary hypertension in systemic lupus Erythematosus. Best Practice & Research Clinical Rheumatology 27 (2013) 425–434
9. F. Lian, D. Chen, Y. Wang *et al.*, “Clinical features and independent predictors of pulmonary arterial hypertension in systemic lupus erythematosus,” *Rheumatology International*. In press.
10. Min HK, Lee JH, Jung SM *et al.* Pulmonary hypertension in systemic lupus erythematosus: an independent predictor of patient survival. Korean J Intern Med 2015;30:232-241
11. A. Cefle, M. Inanc, M. Sayarlioglu *et al.*, “Pulmonary hypertension in systemic lupus erythematosus: relationship with antiphospholipid antibodies and severe disease outcome,” *Rheumatology International*, vol. 31, no. 2, pp. 183–189, 2011.
12. VV McLaughlin, SL Archer, DB Badesch *et al.*, “ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association,” *Journal of the American College of Cardiology*, vol. 53, no. 17, pp. 1573–1619, 2009, *Circulation*, vol. 119, no. 16, pp. 2250–2294.