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Pulmonary Hypertension As Initial Presentation Of Systemic Lupus Erythematosus: A Rare Case Report

Rizqi Arini Siregar*[1] , RM Suryo Anggoro Kusumo Wibowo[1]

[1]Department of Rheumatology Division Internal Medicine, Faculty of Medicine, Internal Medicine Department Dr Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Abstract:

Backgrounds: SLE is a disease with diverse manifestations and occurred 6-10 times more often in women than men. Pulmonary hypertension (PH) has been reported as clinical manifestations of SLE and its prevalence is estimated between 0.5% and 43%. However, PH as the presenting manifestation of SLE is rarely reported. SLE patients with PH has an unfavorable prognosis with the median survival from the onset of PH is two years.

Aim: To report a case of 37-year-old woman with PH as the presenting manifestation of SLE and review the literature about such case.

Cases: A 37 years old female patient was admitted with the main complaint of worsening shortness of breath since one week before. She experienced lassitude and felt more comfortable sleeping with 2 or 3 pillows. She also experienced nausea and edema at her lower extremities. From the physical examination she was slightly jaundice, non-scarring alopecia, mild bilateral pitting edema and holosystolic murmur were also found. Her Antinuclear Antibody (ANA) test was positive with 1/320 titer and low complement level. Chest X-ray showed cardiomegaly. Echocardiography and aortic CT scan showed pulmonary hypertension. She fulfilled 2019 ACR/EULAR criteria for SLE and was diagnosed as SLE-associated pulmonary hypertension (SLE-a PH). She was treated with anticoagulant, glucocorticoid, antimalarial, immunosuppressive agent and standard treatment of PH with improving symptoms.

Conclusion: Pulmonary hypertension is a rare initial manifestation of autoimmune disease including SLE

Keyword: autoimmune disease, Pulmonary hypertension, SLE

Introduction:

Systemic Lupus Erythematosus is one of known autoimmune diseases. It possesses various clinical manifestations, but the three main symptoms are generally always present: extreme fatigue, skin rash, and joint pain.[1] There are more than 5 million people with SLE, and there are more than 100 thousand new cases occur every year worldwide with the general prevalence of 1-5 people per 100,000 population.[2] Women are 6-10 times more often than men, especially during the second to fourth decades of life.[1,2] The etiology of SLE is not completely explained but genetics, infection, utilization of drugs, exposure to sunlight, sex hormones, and stress may have important roles.[3] The clinical manifestations of SLE is diverse and can affect many organs including joints, skin, and also internal organs including kidney or the lung.[1]

Lung involvement in SLE can present as pleural effusion, pulmonary hemorrhage, or pulmonary hypertension. Pulmonary arterial hypertension (PAH) is a dangerous complication of SLE and may hamper the disease outcomes.[4] The prevalence of PH in SLE approximately ranges from 0.5% to 43% according to 1366 published articles which includes 23 meta-analysis. The wide range of prevalence are caused by the differences in study designs, diagnostic criteria and characteristics of subjects in those studies.[5]

The pathophysiology of PAH related to SLE are complex and involving a combination of vasoconstriction, remodeling of vessel wall, and thrombosis which leads to elevated pulmonary arterial pressure.[1] Various pathogenic mechanisms have been hypothesized for the occurrence of SLE-a PAH, in which genetic susceptibility, immune system dysregulation, and external cues such as infection play key roles. Increased vasoconstriction due to raised endothelin-1 and thromboxane A2 levels combined with decreased levels of the vasodilator prostacyclin can cause imbalance between vasoconstriction and vasodilation which resulted in hypoxia, increased vessel wall pressure, and stimulation of the endothelium.[6] This pulmonary vasoconstriction results in hypoxia along with expression of several hypoxia-induced factors and erythropoietin, leading to pulmonary vascular smooth muscle proliferation and vasculature remodeling, inflammatory cells activation and inflammatory cytokines release. All the above conditions disrupt endothelial function and cause further vascular remodeling which contributes to thromboembolic disease, especially observed in patients positive for antiphospholipid antibodies, leading to a hypercoagulable state.[7]

Study by Zhang et al. reported that the presence of PAH is related to worse disease course in SLE patients. Serositis, anti-RNP antibody positivity, or DLCO/%Pred<70% might accompany SLE-a PAH in 292 patients in their study even if the SLE itself is stable according to SLE disease activity index. Therefore early screening of SLE-a PAH using transthoracic echocardiography (TTE) was urged for patients who have serositis, anti-RNP antibody positivity, or DLCO/% pred <70%. Additional procedure such as right heart catheterization (RHC) is necessary to confirm the diagnosis of PAH. Prompt treatment and follow up are mandatory for a patient once the diagnosis of SLE-aPAH is established.[6]

Unfavorable outcomes are likely to occur in patients with SLE and PH. Condliffe et al conducted a study in 20 SLE patients with PH, of which 55% received follow-up therapy for PAH. They found that median survival was 13 months.[8] Another literature stated that patients with SLE

and PH had 5-year survival of 60.2% compared to 97.8% in their counterparts. However, with advancement in therapeutic approaches, the median survival of SLE-a PH patients is improved from less than three years to a more than 90% of 2-year survival.[1] Here, we would like to report a 37-year-old woman with complaints of PH as the presenting manifestations of SLE.

Case Reports:

A 37 years old female patient came to our emergency unit with the main complaint of worsening shortness of breath since one week before. She experiences breathlessness during exertion, lassitude and felt more comfortable sleeping with 2 or 3 pillows. She also experienced nausea and edema at her lower extremity. No history of chest pain, fever, or cough. She also experienced hair loss for six months. She denied complaint of myalgia, joint pain, rash on her face or skin, mouth ulcer, Raynaud phenomenon and skin thickening. She is a married woman with three children, with no history of miscarriage. Hypertension, diabetes, and any other diseases were denied.

From physical examination she was fully alert, with blood pressure 108/79 mmHg, heart rate 79 times per minute, respiratory rate 30 times per minute, and normal temperature. Her peripheral oxygen saturation was 98% without oxygen supplementation. Her sclera was icteric. From lung examination there was vesicular breath sound without crackles. There was non-scarring alopecia on her scalp but there was no rash on her skin. From cardiac examination we found regular rhythm, holosystolic murmur at mitral valve without gallop. Other physical examination were unremarkable. From the laboratory evaluations there was elevated C-Reactive protein (CRP) (12.9 mg/dl with normal range of 1.0-10 mg/l), Antinuclear Antibody (ANA) test was positive with 1/320 titer and spindle fiber pattern. Her C3 complement was low (64 mg/dl with normal range of 90–180 mg/dl) but her C4 level and anti dsDNA test were normal. Her urine test showed albuminuria but without abnormal urinary sediment. Her Activated Partial Thromboplastin Time (APTT) was prolonged (54.5 seconds with normal value of 33.2 seconds) with high D Dimer (4170 ng/ml with normal value of <500 ng/ml) and her lupus anticoagulant was positive. Her liver function test was abnormal with increased total bilirubin (3.44 mg/dl with normal range between 0.2 and 1.2 mg/dl), and increased direct bilirubin (1.95 mg/dl with normal range of 0.3-1.2 mg/dl). From her sputum we found gram-negative and positive bacteria, and negative test for tuberculosis.

Her chest X-Ray showed cardiomegaly (**Figure 1**). Echocardiography examination showed right ventricle (RV) dilatation and hypertrophy, concentric remodeling on left ventricle (LV) wall with D-shaped septum. The kinetic of left ventricle (LV) was normal with ejection fraction of 62.3%. There was severe tricuspid regurgitation (TR) and mild-moderate pulmonary regurgitation (PR). The LV systolic function was good, but there was grade I diastolic dysfunction. RV systolic function was good. Tricuspid Annular Plane Systolic Excursion (TAPSE) was 17.8 with cardiac output (CO) 2.58 L/minute and stroke volume (SV) 36.7, with no thrombus. There was moderate pericardial effusion (1.73 cm) and collapse of systolic RA and diastolic RV, thickening pericardial, and high probability of PH.

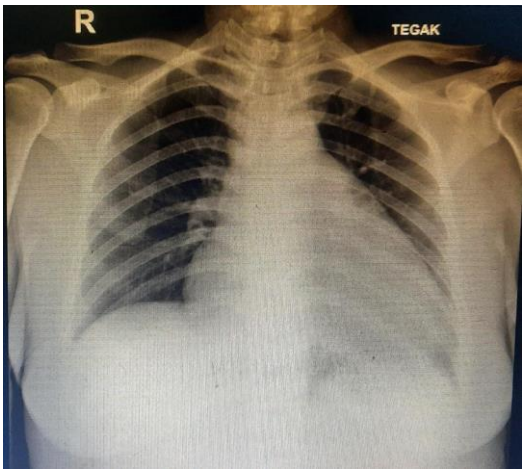

Figure 1 X-Ray showed cardiomegaly

Abdominal ultrasonography found congestive liver disease, chronic cholecystitis, right pleural effusion, and minimal ascites. Thorax CT scan showed cardiomegaly with pulmonary hypertension and pericardial effusion, pleural effusion with compressive atelectasis on inferior lobe of the right lung with no abnormalities on lung parenchyma. The result of the CT scan of the thoracic aorta showed cardiomegaly, dilatation of pulmonary trunk with increased ratio of pulmonary trunk and ascending aorta which suggest pulmonary hypertension, pericardial effusion, pleural effusion on right posterior hemithorax, no filling defect on pulmonary artery and vein. Pleural effusion analysis showed transudate, with positive Rivalta test, low serum protein, low pleural fluid LDH, and negative Adenosine Deaminase (ADA) test. Based on these findings the patient fulfilled the 2019 ACR/EULAR SLE classification criteria with the total score of 12 (non-scarring alopecia, pleural or pericardial effusion, lupus anticoagulant positive and low C3). We diagnosed this patient as Pulmonary Hypertension associated with SLE (SLE-a PH) with moderate disease activity based on Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 10, congestive hepatopathy and coagulopathy suspected due to congestive hepatopathy or due to positive lupus anticoagulant. We treated this patient with subcutaneous Enoxaparin 0,5 mL, intravenous Furosemide 40 mg twice daily, subcutaneous unfractionated heparin 5000 IU every 12 hours, oral Beraprost 20 mcg every 8 hours, methylprednisolone 24 mg per day, hydroxychloroquine 200 mg daily, sildenafil 50 mg per day and mycophenolic acid 360 mg twice daily. Her clinical symptoms was improved after 3 days of treatment and she was discharged from hospital on the 7th day.

Discussion:

Our study reported a female patient aged 37 years with PAH as a initial manifestation of SLE who was received vasodilator and mycophenolic acid. The patient had no history of cardiovascular risk factors, portal hypertension or congenital heart disease. She had always enjoyed good health until 1 week before admission, when she started to experience worsening shortness of breath and diagnosed with SLE-aPH. The SLE-aPH prevalence has been estimated to range between 0.005 to

14% based on cardiac catheterisation as the gold standard of diagnosis.[1] There were only few case reports published regarding this condition.

In this report, the presenting manifestation of the patient was worsening shortness of breath during exertion and lassitude. From SLE manifestations, she experienced a lot of hair loss for six months. A study by Kiani et al reported a 32 years old female with SLE-aPH that visited primary care physician with chief complaints of progressively worsening breathlessness on exertion and edema on both lower extremities. This patient experienced cardiogenic shock after underwent a pericardial window. She did not experience any symptoms of SLE before, except fatique.[1] Study by Prete et al reported a severe PAH case in a female aged 32 years with sudden onset of exertional dyspnea, accompanied by chest pain and palpitation as initial manifestation of PH. She also experienced generalised arthralgias, continuous-remittent fever and increasing weakness as SLE manifestation.[9]

Patients with SLE and PH tend to have positive result of ANA, ACL and RNP. Anti-ACL antibody was positive in 198 (46.6%) patients of 14 studies. A total of 51.3% (46.2–56.8%) SLE patients with PH from five studies tested positive for anti-ACL antibodies compared to only 23.8% (16–28.9%) of their counterparts. There was a positive correlation between anti-ACL antibody and PH based on TTE result.[4] Several markers in association with disease outcomes, particularly mortality, of PAH have been identified. Serum uric acid, BNP, and NT-pro BNP levels are among the identified biomarkers. Regardless severity of PH, cardiac troponin T plays role as is an independent predictor of mortality in the sufferers. Plasma vWF and D-dimer are other biomarkers associated with mortality in patients with PH. There is no single most accurate biomarker. The combination of several biomarkers such as brain natriuretic peptide, N-terminal probrain natriuretic peptide and troponin T, may become part of the standard work-up and follow-up of pulmonary arterial hypertension since there are growing evidences supporting their utilization in patient's management.[3,10] The identification of specific predictive markers with a higher specificity and sensitivity than those currently available, is urgently needed. Such biomarkers, in association to echo doppler echocardiography, should also ideally allow a certain diagnosis to be made without the aid of right heart catheterisation, which is still the gold standard despite its invasive nature.[3,11]

In our patient, the diagnosis of PH was established with combination of clinical findings, aortic CT scan and echocardiography. We did not conduct the anti RNP and right heart cardiac catheterization that can be the limitation of this report. Study by Kiani et al did the chest X-ray, CT chest and echocardiogram that showed pulmonary edema and pericardial effusion and severe right heart chambers dilation. Urgent right heart catheterization (RHC) was conducted to the patient and the results were severe pulmonary arterial hypertension (PAH) marked by elevated pulmonary arterial pressure (PAP) (97/52 mmHg), normal pulmonary artery wedge pressure (PAWP) (14 mmHg), and decreased cardiac output (CO) (3.61 L/min). The results pointed to the diagnosis of primary PH. Laboratory examinations showed elevation in anti-nuclear antibody (ANA) titre of 1 : 640 from normal value of <1 : 40, positive antibodies against nuclear proteins (double-stranded DNA, SSA, SSB, abd Smith), and decreased serum complement C3 and C4 levels. Anti- phospholipid

antibody syndrome was excluded from initial workups.[1] Study by Prete et al reported that the patient conducted a trans-thoracic echocardiogram revealed enlargement and overload of the right heart. Right heart cardiac catheterisation revealed a sPAP of 76 mm Hg and mPAP of 52 mmHg. ANA along with antibody against dsDNA, SSA, Sm and RNP were also positive in this patient, whereas antiphospholipid antibodies and lupus anticoagulant were negative. The patient also had high N-terminal pro-brain-natriuretic peptide (NT-pro BNP) and D-dimers levels.[9]

The therapeutic approach in managing SLE-aPH includes anticoagulants, immune suppresant, oxygen and vasodilators. However, managing patients with CTD-associated PAH is more difficult and sophisticated compared to Idiopathic Pulmonary Arterial Hypertension (IPAH). The algorithm is similar for both conditions but combination of immunosuppressive agents i.e. glucocorticosteroids and cyclophosphamide gives better clinical improvement in patients with PAH associated with SLE or mixed CTD.[6] Early, intensive treatment for SLE is crucial to improve outcomes.[1]

There are a wide range of drugs utilized to treat SLE-aPH including corticosteroids, immunosuppressants, vasodilators, endothelin receptor antagonists and anticoagulants.[1] Anticoagulants are necessary for patients with SLE-aPH due to increased risk of thrombosis. The increased risk is caused by chronic hypoxia and hypercapnia which result in polycythemia. Polycythemia leads to increased coagulation activity and stasis of microcirculation which ends with thrombosis and embolism.[12] However, the effect of warfarin anticoagulation is still in debate since there is not enough evidence supporting the benefit of anticoagulant administration for patients with SLE–aPH.[13] Further study is mandatory to illuminate this issue.

We treat this patient with Mycophenolic Acid (MPA) with initial dose of 360 mg twice a day per oral. Previous study by Prete et al reported that Mycophenolate Mofetil (MMF) (1g/die), cyclosporine (150 mg/die), sildenafil and bosentan, epoprostenol, and corticosteroid were given to their patient with good clinical improvement.[9] Study by Kiani reported that her patient was given prostacyclin infusion, solumedrol 500 mg IV two times in a days, hydroxychloroquine 200 mg once daily, cyclophosphamide 500 mg IV, therapeutic plasma exchange (TPE) and planned to heart-lung transplant evaluation. Unfortunately the patient's clinical condition was worsening and the patient passed away.[1]

Mycophenolate mofetil (MMF) contains precursor of mycophenolic acid (MPA). This agent has been used to treat various connective tissue diseases due to it's immunosuppression property. Besides, MPA also has the ability to inhibit other cells' proliferation including vascular endothelial cells. In the case of SLE-aPH, MMF utilization is shown to lower right ventricle systolic pressure effectively. This is followed by amelioration of right ventricular hypertrophy and thinning of pulmonary arteries' medial layer. Furthermore, MMF suppresses proliferation of proliferating cell nuclear antigen (PCNA)-positive cells and interrupts macrophages infiltration. It also decreases the expression of mediators such as P-selectin and interleukin-6 on the endothelial cells of pulmonary arteries. The development of PAH may be halted by both anti-inflammatory and anti-proliferative properties of MMF as stated above.[14]

As stated before that the combination of corticosteroids and immunosuppressive agents gives significantly better outcome, utilization in patients with early stage PH will result in more favorable outcome.[15] The function of lungs and heart can also be restored by using pulmonary vasodilators.

Calcium channel blockers (CCB) are primary option for patients who responses significantly with vasodilator. High dose of CCB may be utilized. Vasodilators may reduce right ventricular overload and result in increased exercise tolerance, improved hemodynamics, and prolonged survival time. Unfortunately, the side effect should be kept in mind particularly hypotension. Hypotension may appear due to reduced systemic vascular resistance. Additionally, vasodilators may increase ventilation/perfusion mismatch.[2] Baseline heart rate of patient may be used as guideline in choosing the suitable CCB. Nifedipine and amlodipine may benefit patients with bradycardia while diltiazem is more suitable for those who have tachycardia. The daily doses for effective management of IPAH are high. For nifedipine, the dose ranges from 120 to 240 mg, for diltiazem the range is 240 to 720 mg while amlodipine's dose reaches 20 mg. Escalation from low starting dose may be applied, e.g. 30 mg of slow-release nifedipine BID or 60 mg of diltiazem TID or 2.5 mg of amlodipine OID. Up-titration the can be done with cautions to maximum dose. Mind the appearance of lower limb oedema and hypotension during the process.[16,17]

The pathogenesis of PAH is influenced by the endothelin system. By binding to it's two distinct receptor isoforms in pulmonary vascular endothelial cells i.e. endothelin receptor type A and B, endothelin-1 elicits vasoconstriction and mitosis.[16] Blocking the binding process with endothelin receptor antagonist such as bosentan results in improvement of clinical manifestations of PH. Bosentan is administered orally and may block both endothelin receptors. Mok et al. found that transient or sustained decrease in systolic PAP along with improvement in six-minute walk distance (6MWD) may be achieved via 12 month of bosentan administration.[17] Unfortunately, endothelin receptor antagonists such as bosentan, ambrisentan and macitentan are not available in Indonesia. Only prostacyclin analogs like beraprost and iloprost and oral PDE-5i like sildenafil which are currently available.[18]

The utilization of prostacyclin analogues and prostacyclin receptor agonists has been widely applied in patients with PAH. Prostacyclin acts as vasodilator and inhibitor of thrombocyte aggregation. The last property may prevent thrombocyte clumping and thrombogenesis in the lungs. The example of these agents are beraprost, epoprostenol, treprostinil, iloprost, and selexipag.[19] Beraprost is the first agent and available in oral preparation. Two RCTs from Europe and USA reported that beraprost improves exercise capacity and this effect lasts for 3–6 months. Iloprost is another agent from this class. It is ready in intravenous, oral, or aerosol preparations.[16] lloprost binds with the IP and EP3 receptor. This triggers pulmonary vasodilation and inhibition of vascular remodelling, inflammation and proliferation.[19]

Other agents for managing PAH are phosphodiesterase type 5 inhibitors (PDE-5i) e.g. sildenafil, and the sGC stimulator e.g. riociguat. Phosphodiesterase type 5 (PDE-5) is an enzyme for degrading cyclic guanosine monophosphate (cGMP). Degradation of cGMP will lower nitric oxide (NO) level and cause vasoconstriction. Inhibition of PDE-5 will reverse the process and lead to vasodilatation. Pulmonary circulation possesses abundant amount of PDE-5 thus the inhibition significantly causes

vasodilatation and improvement in PH clinical manifestations without decreasing systemic arterial pressure. Sildenafil is an example of orally active PDE-5i.[16]

Both monotherapy and combination therapy of several drugs have been applied in patients with PAH. Literature showed that combination therapy is more widely adopted. Approximately 46–75% IPAH cases, 29–50% PAH-CTD cases and 17–32% congenital heart disease-associated PAH have used combination therapeutic approach.[19] A study by Daisuke et al involving 6 adults patients with PH reinforced the previous study. A combination of sildenafil and beraprost resulted in a 2.2-fold greater reduction in mean pulmonary arterial pressure and a 1.6-fold greater reduction in pulmonary vascular resistance compared with beraprost alone. Additionally, this effect persisted longer in combination therapy compared to monotherapy. There was no adverse effect from combination therapy with sildenafil and beraprost, stressing that this is and effective and safe to be administered in patients with PH, at least in the acute phase.[20]

Conclusion:

We reported a case of 37 years old woman with PH as an initial presentation of SLE. The diagnosis of PH in this patient was made by combination of clinical findings, aortic CT scan and echocardiography. Patient had a good clinical response with combination of anticoagulant, glucocorticoid, antimalarial, immunosuppressive agent and standard therapy for PH such as PDE-5 inhibitor.

Conflict of interest

No potential conflict of interest relevant to this article was reported

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