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Pulmonary Abnormalities in Systemic Lupus Erythematosus Patients: A Literature Review

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which the immune system attacks the body's own tissues and organs, causing systemic inflammation. SLE has diverse clinical manifestations and can involve various organs of the body, including the lungs. Although the exact prevalence is unknown, pulmonary involvement can occur in 50-70% of SLE patients and shows clinical symptoms in 4-5% of cases. A thorough understanding of the pulmonary manifestations of SLE can help facilitate early diagnosis and prevent the disease from progressing to a serious condition. The existence of knowledge related to pulmonary abnormalities in SLE patients can also be a consideration in making a diagnosis and choosing the right therapy to improve the patient's quality of life.

Keywords: systemic lupus erythematosus; pulmonary abnormalities; autoimmune.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which the immune system attacks the body's own tissues and organs, causing systemic inflammation. Genetic predisposition, environmental factors, and hormonal influences interact in the development of disease activity. SLE has clinical manifestations and patterns of organ involvement that are so broad and heterogeneous that it is often referred to as a disease of a thousand faces. SLE can involve almost every organ and apparatus with varying severity, from very mild disease without major organ involvement to severe life-threatening conditions [10].

Based on the results of a systematic review with a meta-analysis approach, the global SLE incidence and newly diagnosed population is estimated at 5.14 (1.4 to 15.13) per 100,000 people per year and 0.40 million in one year. Recent data from the CDC registry in Olmsted, Minnesota, USA, showed an increase in the prevalence and incidence of SLE over four decades. The results showed that there was a 2% annual increase in incidence, from 3.3 per 100,000 population from 1976-1988 to 6.4 per 100,000 population from 2009-2018 [3,17].

SLE has diverse clinical manifestations and can involve various organs. The clinical manifestations with the highest incidence are musculoskeletal (53-95%) and mucocutaneous (55-85%) manifestations (Cojocaru et al., 2011). Although the exact prevalence is unknown, pulmonary involvement may occur in 50-70% of SLE patients and present clinically in 4-5% of cases. A US multiethnic cohort study reported that 7.6% and 11.6% of patients had permanent lung damage 5 and 10 years after SLE diagnosis, respectively. SLE patients with pleuropulmonary involvement have been shown to have a significantly lower survival rate than those without pleuropulmonary involvement [16].

An in-depth understanding of the pulmonary manifestations of SLE can help facilitate early diagnosis and prevent the disease from progressing to a serious condition. The existence of knowledge related to pulmonary abnormalities in SLE patients can also be a consideration in making a diagnosis and choosing the right therapy. Therefore, the author has an interest in further discussing pulmonary disorders in SLE patients which is expected to be a source of information regarding the morbidity and mortality of pulmonary disorders in SLE patients.

DEFINITION AND EPIDEMIOLOGY

Systemic lupus erythematosus is a chronic autoimmune disease in which the immune system attacks the body's own tissues and organs. SLE has diverse clinical manifestations, causative factors, immunological and laboratory abnormalities, and disease course. This is why SLE can affect various tissues and organ systems with mild to severe symptoms. Symptoms of SLE may appear suddenly, develop slowly, last for a long time, or be temporary before relapsing [9,10].

The prevalence and incidence of SLE are highest in North America at 23.2/100,000 population/year and 241/100,000 population, respectively. Based on gender, women have more incidence than men with a ratio of 2:1 to 15:1. The number of people with lupus in Indonesia has not been confirmed. According to the 2016 online Hospital Information System data recorded by the Data and Information Center of the Indonesian Ministry of Health, there were 2,166 inpatients diagnosed with lupus from 858 hospitals that reported their data. This number has almost doubled from 2014, which was 1,169 patients [10].

PATHOGENESIS

SLE is labeled “the cruel mystery” by the Lupus Foundation of America. The nickname is certainly inseparable from its complex and intricate clinical manifestations and etiopathogenesis. In general, the pathogenesis of SLE involves complex interactions between environmental factors and the genome resulting in epigenetic changes that lead to altered expression of specific genes that contribute to disease progression. Exposure to environmental factors such as UVB radiation, infections, and toxins triggers loss of immune tolerance in genetically susceptible individuals and leads to aberrant activation of autoimmunity [2].

Genetics

Genetics plays an important role in predisposing to the development of SLE. Although most SLE is polygenic, it can also be based on homozygous single-gene mutations. However, in many cases, the occurrence of these predisposing genes cannot always be attributed to SLE. Diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis, suggest the possibility of a common genetic influence with autoimmune responses [11].

Gender

SLE is more prevalent in women, with a female-to-male ratio of 9:1. This is attributed to the tendency of women to produce more estrogen. Estrogen expressed on immune cells has been reported to enhance humoral responses and maintain B cell autoreactivation. However, an imbalance in estrogen production, in this case excessive estrogen levels, can activate the production of autoantibodies that are responsible for damaging the body's own tissues in autoimmune diseases [4].

Environment

Several biological, physical, and chemical agents have been associated with an increased risk of development and/or progression of SLE. Among biological agents, Epstein-Barr virus infection has long been proposed to be associated with SLE, while for physical agents, a known risk factor is exposure to ultraviolet light, especially UVB, which can damage DNA and promote cell apoptosis thereby favoring antigen presentation to immune cells [4].

Immune Dysregulation

Immune dysregulation in SLE is reported to form poorly controlled autoantibodies. These antibodies can bind to self-antigens and form immune complexes that trigger tissue injury and ultimately lead to further cell death. This process along with local inflammatory mediators will trigger an autoimmune process [2].

DISEASE ACTIVITY

Assessment of SLE disease activity is needed as a basis for determining therapy for each individual. This assessment is done from the beginning of diagnosis using several instruments such as the Physician's Global Assessment, systemic lupus erythematosus disease activity index (SLEDAI), Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), and the British isles lupus assessment group (BILAG) [13].

The SLEDAI was first introduced in 1985 as a global index to assess SLE disease activity over the past 10 years. The SLEDAI consists of 24 clinical and laboratory variables covering nine organ systems. Each variable has an operational definition and a score of 1-8. SLEDAI scores are divided into five, namely, no disease activity (score 0), mild disease activity (score 1-5), moderate disease activity (score 6-10), severe disease activity (score 11-19), and very severe disease activity (score ≥20). In addition to determining disease activity, SLEDAI is used to determine disease outcome or recurrence (score increase >3), improvement (score decrease >3), persistent active (score change ± 1-3), and remission (score 0) [12].

MEX-SLEDAI is easier to apply in health services that do not have sophisticated laboratory facilities such as DNA, immunology, and complement testing. MEX-SLEDAI scores are categorized into remission (score 0-1), mild (score 2-5), moderate (6-9), severe 10-13), and very severe (≥14) [12].

In terms of assessing disease activity from pulmonary manifestations in SLE, BILAG has a cardiorespiratory subsection that considers pulmonary disorders such as pleuritis, pleural effusion, pulmonary hemorrhage/vasculitis, interstitial lung disease, and shrinking lung syndrome as possible pulmonary manifestations in SLE patients. In comparison, SLEDAI only considers pleuritis as a visible manifestation of lupus activity involving the lung. This may result in some SLE patients with respiratory complications being considered in remission or a state of low disease activity [14].

DIAGNOSIS

The diagnosis of SLE can be made based on clinical symptoms and supporting examination results. In 2019, the European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) published SLE classification criteria divided into 10 major groups. In these criteria, there is an entry criterion of a positive ANA test result, which means that the 10 major groups in the EULAR/ACR criteria only apply to patients with a positive ANA test result. After meeting the entry criteria, patients can be said to be classified as SLE if they have a total score of 10 or more and meet at least one clinical criterion. In addition, in 2012 SLICC also released SLE classification standards consisting of 17 criteria. Of the 17 criteria, patients are said to be included in the SLE classification if they meet at least 4 criteria accompanied by at least 1 clinical criterion and 1 immunological criterion. According to a validation study, the SLICC-2012 classification criteria have a higher sensitivity with a percentage of 87.3% compared to EULAR/ACR 2019 with a percentage of 86.1% [16].

TREATMENT AND MANAGEMENT

Management of SLE patients requires a holistic approach that includes education, rehabilitation programs, and medical therapy. The management of SLE aims to achieve remission and prevent relapse. If remission cannot be achieved, the goal of treatment is to achieve a lupus-low disease activity state in all organ systems. The long-term goals of SLE management are to prevent organ damage, prevent comorbidities, avoid or reduce the risk of drug toxicity, and maintain optimal quality of life [9].

Education

Patient education is an important part of SLE management. All patients diagnosed with SLE should receive education from health professionals. The education provided should also include the patient's family. Educational materials that can be given by doctors to patients with SLE include an explanation of SLE and organs that may be affected, healthy lifestyles, things to avoid, symptoms of recurrence, and the use of drugs and their types [9].

Rehabilitation Program

SLE patients tend to have a reduced aerobic capacity of about 30-40%. SLE is often associated with fatigue, cardiovascular risk, obesity, musculoskeletal symptoms, sleep disturbances, and reduced quality of life. Therefore, SLE patients should be encouraged to actively participate in physical activities to train muscle strength and improve physical endurance without putting additional stress on the joints [9].

Pharmacotherapy

Pharmacotherapy is given according to the organs involved with the aim of reducing systemic inflammation and achieving remission. In addition, drug selection is also tailored to the degree of SLE disease based on the patient's clinical manifestations or SLEDAI/MEX-SLEDAI score [9].

TABLE 1: Medications for The Management of SLE [9].

	Mild SLE	Moderate SLE	Severe SLE
Initial Therapy	Oral prednisolone ≤20 mg/day for 1-2 weeks or Methylprednisolone Injection 80-120 mg IM/IA, AND HCQ ≤6.5 mg/kgBB/day*, and/or MTX 7.5-15 mg/week, and/or NSAIDs as symptomatic.	Prednisolone ≤0.5 mg/kgBB/day with or without injection Methylprednisolone ≤250 mh IV/day for 3 days, AND AZA 1.5-2.0 mg/kgBB/day or MTX 10-25 mg/week or MMF 2-3 g/day** or MPA 1.44-2.16 g/day or Cyclosporine ≤2.0 mg/kgBB/day, AND HCQ ≤6.5 mg/kgBB/day	Prednisolone ≤0.5 mg/kgBB/day and Methylprednisolone injection 500-750 mg IV/day for 3 days OR Prednisolone ≤0.75-1 mg/kgBB/day AND AZA 2-3 mg/kgBB/day or MMF 2-3 g/day** or MPA 1.44-2.16 g/day or Cyclosporine ≤2.5 mg/kgBB/day or CYC IV*** AND HCQ ≤6.5 mg/kgBB/day
Maintenance	Prednisolone ≤7.5 mg/day, AND HCQ 200 mg/day, and/or MTX 10 mg/week, AND use of sunscreen and education to wear sun-protective clothing *Description:* If stable/remission, targeted to stop all drugs except HCQ	Prednisolone ≤7.5 mg/day, AND HCQ 200 mg/day, AND AZA 50-100 mg/day or MTX 10 mg/week or MMF 1 g/day* or cyclosporine 50-100 mg/day *Description:* If stable/remission, targeted to stop all drugs except HCQ In refractory cases, belimumab or rituksimab may be considered.	Prednisolone ≤7.5 mg/day, DAN HCQ 200 mg/day, DAN AZA 50-100 mg/day or MMF 1.0-1.5 g/day* or cyclosporine 50-100 mg/day *Description:* If stable/remission, targeted to stop all drugs except HCQ If the patient does not respond well to immunosuppressants, belimumab or rituksimab may be considered.

Description: AZA: azathioprine, CYC: cyclophosphamide, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug, IA: interarticular, IM: intermuscular, *or chloroquine (CQ) ≤3mg/kg BW/day, ** 1 g MMF dose equivalent to 720 mg mycophenolic acid (MPA), *** CYC IV 500mg/2 weeks for 6 doses or 500-1000 mg/m2 monthly for 6 months.

PULMONARY ABNORMALITIES IN SLE PATIENTS

Pulmonary abnormalities in SLE patients can be acute or chronic, primary (caused by SLE itself) or secondary (e.g. infection, drug toxicity, atopic disease, and malignancy). Acute abnormalities may be associated with generalized lupus disease activity, while chronic abnormalities may develop independently of generalized disease activity [2].

Primary Lung Disease

SLE is an autoimmune disease that attacks connective tissue and most commonly involves the lungs. At least once during the course of the disease, 50% of SLE patients have pleural and/or pulmonary manifestations, leading to increased morbidity and mortality. Respiratory system involvement in SLE is important to consider, as respiratory involvement may present asymptomatically. Pulmonary manifestations in SLE include disorders of the lung parenchyma, pleura, and pulmonary vasculature [8].

• *Interstitial Lung Disease*

The prevalence of interstitial lung disease in patients with SLE ranges from 3-9%. Various forms of SLE-associated ILD include Non-Specific Interstitial Pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia, follicular bronchitis, and ordinary interstitial pneumonia. SLE patients with manifestations of ILD mostly complain of similar symptoms, such as dry cough and dyspnea, although it is important to consider that some may be asymptomatic. Diagnosis can be made with High-Resolution Computed Tomography. Radiologic features in the early stages are generally normal or show irregular linear opacities. Some studies also mention findings of diffuse or bibasal infiltrates, pleural disease, honeycombing, and decreased lung volumes. High Resolution Computed Tomography can be used to corroborate the presence of interstitial disease and classify it according to the observed pattern. For now, the treatment is to administer high-dose corticosteroids along with agents such as cyclophosphamide and rituximab in severe cases with the aim of inducing remission [1].

• *Pneumonitis Lupus*

The prevalence of acute lupus pneumonitis in SLE patients ranges from 1-4% with a mortality rate of up to 50% in acute episodes. Approximately 50-100% of patients who have recovered from the acute episode tend to progress to chronic interstitial pneumonitis. Clinical manifestations of acute lupus pneumonitis are characterized by fever, cough, dyspnea, pleuritic chest pain, and hypoxemia, and are sometimes accompanied by hemoptysis. Physical examination may show tachycardia, tachypnea, hypoxemia, hypocapnia, and ronki. Radiologic examination shows unilateral or bilateral infiltrates mainly in the inferior lobe of the lung, with or without pleural effusion. However, chest X-rays can also show a normal picture, especially in the early phase, or only show pulmonary nodules.

The prognosis of SLE patients with acute lupus pneumonitis is poor with a high risk of mortality. Factors that are considered to contribute to the worsening of the patient's condition include co-infections, aspiration, diaphragmatic dysfunction, cardiac and renal failure, and drug toxicity. Corticosteroid administration is the main therapy that can be performed. In severe cases, methylprednisolone 1-1000 mg/day for 3 days may also be an option, followed by prednisone 1-2 mg/kg per day with the principle of tapering off [1,5].

• *Diffuse Alveolar Hemorrhage*

The prevalence of diffuse alveolar hemorrhage in SLE patients ranges from 0.5-0.6% to 5.4-5.7% with a female-to-male ratio of 6:1. The clinical picture of diffuse alveolar hemorrhage is characterized by sudden onset, dyspnea, hypoxemia with possible acute respiratory failure, fever, cough, and hemoptysis leading to a rapid decrease in hemoglobin levels and the appearance of alveolar infiltrates or interstitial infiltrates. Laboratory findings may show a rapid decrease in hemoglobin levels along with other characteristics of active SLE, such as low complement levels, thrombocytopenia, and autoantibodies. A rapid drop in hematocrit levels should also be noted. Chest X-ray may be normal or show bilateral features and airspace opacities (patchy, focal, or diffuse). A CT scan may show diffuse, bilateral, alveolar infiltrates with ground glass opacities or diffuse nodular opacities which is more accurate than a chest x-ray. BALF is generally hemorrhagic and can be used as a diagnostic criterion for diffuse alveolar hemorrhage if there are 20% or more macrophages containing hemosiderin [1]

• *Pleuritis*

Pleuritis is the most frequent pulmonary manifestation in SLE patients and is the only pulmonary manifestation currently included in the 1997 American College of Rheumatology classification criteria for SLE. Clinical features of pleuritis vary from asymptomatic, incidental findings on imaging, to pleuritic chest pain that increases with deep inspiration. The diagnosis of pleural involvement in SLE is clinically linked to the patient's history. However, it is important to eliminate other causes of pleural inflammation that can occur in SLE including infection, pulmonary embolism, malignancy, congestive heart failure or pericarditis. Aspiration may be performed when there is clinical uncertainty in determining the cause of pleural effusion. Pleural fluid in SLE patients classically shows increased levels of protein, lactate dehydrogenase, leukocytes, and a positive ANA test in some cases. Radiologic examination shows a radiopaque appearance and a blunt costophrenic angle, compatible with pleural effusion. In mild cases of pleurisy, short-term NSAID non-steroidal anti-inflammatory drugs may be used to control symptoms. Systemic corticosteroids may also be given in severe cases. For more severe cases and in refractory cases, the use of azathioprine, methotrexate, mycophenolate,

cyclophosphamide, intravenous immunoglobulin, and cyclosporine may also be an option [1,5,18].

• *Pulmonary Embolic Disease*

SLE patients have a higher risk of deep vein thrombosis, which has occurred in 10% of patients, and pulmonary embolism with a 3-fold increased risk compared to the general population. Pulmonary embolism has a high mortality rate of up to 15%. You et. al in their study found risk factors associated with pulmonary embolisms, such as high body mass index, hypoalbuminemia, positive anti-phospholipid antibodies, high levels of C-reactive protein, and the use of high doses of corticosteroids (>0.5 mg/Kg/day). The clinical symptoms that occur depend on the severity of the blood vessel occlusion. Symptoms of pulmonary embolism that can appear such as chest pain, pleuritic, dyspnea, hemoptysis, tachypnea, and tachycardia. Chronic pulmonary embolism can develop into secondary pulmonary arterial hypertension. Computed Tomography Pulmonary Angiogram is the gold standard in diagnosis. The imaging technique can identify thrombosis in the pulmonary vasculature. Anti-phospholipid syndrome therapy can use anticoagulants with vitamin K antagonists. In patients with recurrent arterial or venous thrombosis, the addition of low-dose aspirin should be considered. In patients at increased risk of anti-phospholipid antibodies without a history of thrombosis, prophylactic treatment with low-dose aspirin may also be an option [5,6].

• *Pulmonary Arterial Hypertension*

Pulmonary arterial hypertension is a progressive disorder characterized by mean pulmonary artery pressure (Mpap) at rest above 25 mmHg and pulmonary wedge pressure (PWP) below 15 mmHg accompanied by increased pulmonary vascular resistance (PVR) above 3 WU. Clinical symptoms of pulmonary arterial hypertension in SLE are often nonspecific and related to right ventricular dysfunction, such as dyspnea, dry cough, fatigue, weakness, angina, syncope, and hemoptysis. Initially, symptoms often appear during exercise, but in advanced cases may occur at rest. Electrocardiogram examination generally shows right ventricular hypertrophy and right axis deviation. Radiographic imaging with computed tomography can be used to exclude other diseases such as ILD and often shows enlarged pulmonary veins. Echocardiography can estimate systolic pulmonary artery pressure so it is a vital non-invasive tool that can be used for diagnosis. However, even if an echocardiogram shows suggestive results followed by high clinical suspicion, right heart catheterization remains the gold standard in diagnosis. The management of pulmonary arterial hypertension in SLE is by administering drugs such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin agonists which have been shown to be effective in managing SLE-related pulmonary arterial hypertension at various degrees [5,6].

• *Shrinking Lung Syndrome*

Shrinking lung syndrome is a rare manifestation of SLE with an estimated prevalence of about 1-2%. The exact cause of shrinking lung syndrome is unknown, but it is believed to involve diaphragmatic abnormalities associated with impaired phrenic nerve signaling. Patients with shrinking lung syndrome often present with symptoms of pleuritic chest pain and progressive dyspnea. As it is a rare manifestation of SLE, there are no diagnostic criteria for shrinking lung syndrome. Radiographic examination in shrinking lung syndrome is nonspecific and often shows diaphragmatic elevation and basal atelectasis with no evidence of interstitial or pleural lung disease. Before making a diagnosis of SLE, it is important to consider other conditions including central nervous system disorders, diaphragmatic paralysis, pulmonary fibrosis, and obesity. Due to the uncertainty of the cause of shrinking lung syndrome, the most appropriate treatment options are also unclear. Most studies show a good response to high-dose corticosteroids (30-60 mg prednisolone daily). Immunosuppressant agents, such as azathioprine and cyclophosphamide may also be an option. The prognosis of shrinking lung syndrome is generally good, with most patients improving or stabilizing with treatment [1].

Secondary Lung Disease

• *Infection*

SLE patients are at high risk of severe infections by both common and opportunistic pathogens, which can affect the lungs, urinary tract, soft tissues, and skin. The increased risk is multifactorial and often associated with alterations in the innate and adaptive immune systems. A historical study reported that prolonged use of immunosuppressants may increase the risk of infection in SLE patients by about 40%. They also reported that SLE patients admitted to the Intensive Care Unit (ICU) had a higher risk of respiratory failure with pneumonia as the most common cause of death. Bacteria are the most frequent agents causing infections in SLE patients, with Streptococcus pneumoniae being the most common cause of respiratory tract infections. Viral infections have also been reported, particularly cytomegalovirus and varicella zoster virus. SLE patients also have a high risk of tuberculosis and microbacterial non-tuberculous infections. Diagnostic workup for infection in SLE patients is difficult, as infection may describe an atypical course due to immunosuppression, plus the presence of pulmonary infection may stimulate a flare. Bronchoscopy with BALF analysis can be useful to isolate the pathogen and initiate targeted therapy. Reduction of immunosuppressive therapy for a short period during antimicrobial therapy can be done in severe cases to enhance the immune response [5,7].

• *Drug Side Effects*

The use of immunosuppressive therapy in SLE is associated with possible pulmonary toxicity.

Drug-induced ILD is the most common form of pulmonary abnormality in immunosuppressed SLE patients. The diagnosis of drug-induced lung abnormalities is made when there is a consistent history with precise timing of onset in relation to drug initiation and discontinuation. This is supported by a radiographic or histopathologic pattern consistent with the pattern expected from a particular drug provided other causes are ruled out. Methotrexate has been reported to be the most frequent immunosuppressive agent resulting in pulmonary abnormalities, which can cause acute, subacute, or chronic toxicity in its clinical presentation. Patients generally recover after discontinuation of methotrexate and administration of corticosteroids, but 10% may progress to pulmonary fibrosis which has been reported to have a mortality rate of 1% [6,9].

CONCLUSIONS

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which the immune system attacks the body's own tissues and organs, causing systemic inflammation. Genetic predisposition, environmental factors, and hormonal influences interact in the development of disease activity. SLE has clinical manifestations and patterns of organ involvement that are so broad and heterogeneous that it is often referred to as a disease of a thousand faces.

The clinical manifestations with the highest incidence are musculoskeletal (53-95%) and mucocutaneous (55-85%) manifestations. Although the exact prevalence is unknown, pulmonary involvement may occur in 50-70% of SLE patients and present clinically in 4-5% of cases. Pulmonary abnormalities in children are less common than in adults. However, they can be a significant feature of the disease and lead to deadly complications of SLE. Various studies have reported that patients with SLE may have vague or absent symptoms of pulmonary dysfunction suggestive of subclinical disease. Pulmonary abnormalities in SLE patients may be primary (caused by SLE itself) or secondary (e.g. infection and drug toxicity). Primary lung disorders include disorders of the lung parenchyma, pleura, and pulmonary vasculature.

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