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A Patient of Systemic Lupus Erythematous (SLE) with Tuberculosis (TB) Pleurisy

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Abstract: ***Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that attacks various body systems. Tuberculous pleurisy is one of the most common manifestations of extrapulmonary TB, Tuberculous pleurisyoccurs due to infection with Myobacterium tuberculosis (MTB) in the pleura. The relationship between SLE and TB is said to be closely related, where in SLE there is an increased susceptibility to TB infection as a result of immunosuppressive conditions or as a result of immunosuppressive therapy in SLE patients themselves. We report a patient newly diagnosed with SLE with TB pleurisy. According to some data obtained, the presence of impaired immune system function in SLE patients is associated with the development of clinical manifestations of TB.***

Keywords: Systemic Lupus Erythematosus, Tuberculous pleurisy

1. Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease in which organs, tissues and cells are damaged mediated by tissue-binding autoantibodies and immune complexes. The highest incidence and prevalence of SLE were found in North America at 23.2/100, 000 population/year and 241/100, 000 population. Based on gender, SLE was more common in women than men (2: 1 to 15: 1 ratio). Based on ethnicity, the incidence of SLE among black population is 31.9/100, 000 population/year, Asian 0.9-4.1/100, 000 population/year and Caucasian 0.3-4.8/100, 000 population/year. The incidence of SLE in children is lower than adults, which is less than 1/100, 000 population/year in Europe and America. The prevalence of SLE in children reaches 6.3/100, 000 population in China. The clinical picture of SLE can change, both in terms of disease activity and organ involvement. The immunopathogenesis of SLE is complex and associated with a variety of clinical features. No single mechanism of action can explain all cases and the initial events that trigger it are still unknown. SLE is caused by interactions between susceptibility genes (including alleles HLADRB1, IRF5, STAT4, HLA-A1, DR3, B8), hormonal influences and environmental factors. The interaction of these three factors will cause an abnormal immune response. The management of SLE requires a holistic approach which includes education, rehabilitation programs as well as non-pharmacological and pharmacological therapies, the target of SLE management is to achieve remission and prevent recurrence.1

Tuberculosis is an important public health problem in the world. In 1992, the World Health Organization (WHO) has declared TB as a Global Emergency. The highest number of cases was in Southeast Asia (35%), Africa (30%) and the Western Pacific (20%). In 2009, it was estimated that there were 250, 000 MDR TB cases, but only 12% or 30, 000 confirmed cases. Indonesia is a developing country in Southeast Asia which is classified as a high burden country related to pulmonary TB. Indonesia is ranked fifth as a country that contributes pulmonary TB after India, China, South Africa and Nigeria, namely India (2.0 million), China (1 3 million), South Africa (530 thousand), Nigeria (460 thousand) and Indonesia (460 thousand). Tuberculosis can involve various organ systems in the body. Although pulmonary TB is the most common, extrapulmonary TB is also an important clinical problem. The term extrapulmonary TB is used for tuberculosis that occurs outside the lungs. Based on the epidemiology extrapulmonary TB is 15-20% of all TB cases, where TB lymphadenitis is the most common form (35% of all extrapulmonary TB).2, 9

The increasing incidence of opportunistic infections in SLE patients is caused by several factors including impaired cellular immunity and decreased phagostitic function as well as the effects of immunosuppressants used as pharmacological therapy in SLE. One of the infections that often occurs in SLE patients is TB, the main cause of the high incidence of TB infection is immunosuppressive therapy and impaired immunity in lupus patients themselves. TB infection and other opportunistic infections cause increased mortality in SLE. Several studies have shown an increasing trend of TB infection among SLE patients, especially in TB endemic countries. In the following, we report a case of a woman with SLE accompanied by TB pleurisy.

2. Cases

The female patient Mrs. Y is 26 years old, a Balinese tribe who came to the ER on October 7, 2021, with the main complaint of shortness of breath. The shortness of breath has been felt since 1 week ago, has worsened since 2 days before being admitted to the hospital, the shortness of breath is getting worse. The patient also complained of pain throughout the body since 1 week ago, the pain in the whole body was felt more and more frequently and the most pain was complained of in both legs. Fever was complained of from 3 days before admission to the hospital, the fever was felt to come and go. He complained of cough from 1 week ago and white phlegm. There is also hair loss, recurrent canker sores and swelling in both legs. There has been a weight loss of 20 (twenty) kg during the last three months.

Past medical history, the patient had previously been hospitalized with a diagnosis of Covid 19 and was treated safely for approximately 2 weeks. History of heart disease, hypertension, diabetes mellitus was denied. Based on the family history of the disease, the patient's family did not have an autoimmune disease. Based on social history, the patient is a private worker, neither smokes nor drinks alcohol.

On physical examination, the patient's consciousness was composmentis, general condition was seriously ill, GCS E4V5M6 with blood pressure 140/90 mmHg, pulse rate 130 times per minute, respiratory rate 28 times per minute, temperature 37.5°C, oxygen saturation 95% of room air and VAS 4 lower limb area. On examination of the head and neck, the eyes found both conjunctiva pale, not icteric, then on examination of the mouth an ulcer with reddish edges, miliary in size on the lip mucosa was found. On examination, the thorax looks symmetrical, the heart S1 and S2 are single, regular. In the lungs, there was decreased pulmonary vesicular sound in the left lung and soft wet rhonchi were heard on both lung apex of the patient. On the abdomen, there was a soft abdomen, normal bowel sounds, no palpable splenic liver and tenderness in the epigastric region and right hypochondria. Furthermore, in the extremity region, edema was found in both lower extremities. Dermatological status in the back region, the palmar part of the manus bilaterally has papules, erythematous plaques, multiple. Other physical examinations were within normal limits.

Complete blood count results showed pancytopenia (Hb 6.6 g/dL, Hct 17.7%, MCV 78.9 fl, MCH 29.7 pg, platelets 76.000 cells/mm3, leukocytes 5300/mm³). Peripheral blood picture with results of bicytopenia, normochromic normocytic anemia, normal leukocyte count, dominated by neutrophil segments, shift to the left, decreased platelet count with giant platelets. On clinical chemistry examination, there was an increase in transaminase enzymes (ALT 22 U/L and AST 42 U/L) and hypoalbuminemia (albumin 1.43 g/dL). The patient's bilirubin level is normal. Meanwhile, normal kidney function examination (ureum 30.8 mg/dL and creatinine 0.73 mg/dL).

Examination of blood electrolytes showed hyponatremia (sodium 126.2 mmol/L), potassium 4.19 mmol/L, chloride 93.3 mmol/L. The results of the ANA (IF) >1: 1000. On urinalysis examination, urine appeared cloudy yellow, protein +1, erythrocytes +1, leukocyte sediment 1-3, erythrocyte sediment 5-8. Electrocardiography (ECG) results describe sinus rhythm tachycardia, 128 beats/minute, low voltage, normoaxis. A chest X-ray showed cardiomegaly (RVH) with pulmonary congestive signs and a right pleural effusion. Pleural fluid function was also performed on the patient and ±2000cc fluid was found to be cloudy yellow (like pus) and then the sample was sent for pleural fluid analysis. The results of the analysis of the patient's pleural fluid obtained cloudy clarity, cell count 389, 000/µL (PMN 80%, MN 20%), total protein 2.92; glucose 10. Then the patient was also tested for ADA and the result was 68.23 U/L.

This patient was diagnosed with pleural effusion dextra et causa TB pleurisy with moderate SLE (MEX-SLEDAI score 8). While being treated, the patient was given methylprednisolone1x250 mg (iv) for 3 days, hydroxychloroquine 1x200 mg (po), azathioprine 1x50 mg (po), antibiotics cefuroxime 3x1 gram (iv) and levofloxacin 1x750 mg (iv), paracetamol flash 3x1 gram (iv), esomeprazole 1x40 mg (iv), vip albumin 3x2 caps (po), caviplex 1x1 tab (po), n-acetylcysteine 3x200 mg (po), albumin transfusion and PRC transfusion. Because from the results of the examination the patient had been diagnosed with TB pleurisy, the patient was given OAT 4FDC 1x3 tab (po).

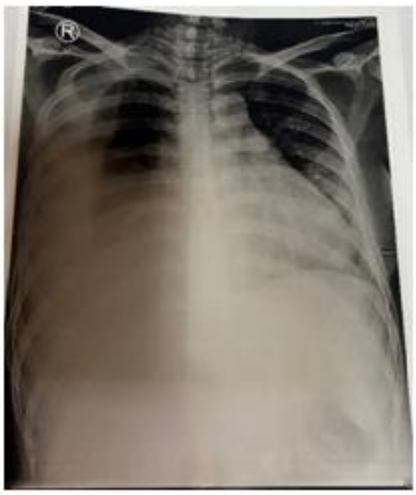

Figure 1: X-ray of the patient's chest, with pleural effusion and cardiomegaly

3. Discussion

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that attacks various body systems. The pathogenesis of SLE is influenced by genetic and environmental factors (such as UV light). The course of SLE begins with a preclinical phase, often mimicking other diseases. Formation and deposition of immune complexes that are increasingly developing cause the course of SLE to enter a more advanced stage with increasingly diverse and multiorgan clinical manifestations. The final stages of the course of SLE are generally caused by long-term complications of SLE that cause organ damage. The main characteristic of SLE is characterized by the emergence of an immune response to endogenous nuclear antigens. Damage to various organs in SLE occurs due to the formation and deposition of autoantibodies and immune complexes. Hyperactive B cells originate from the stimulation of T cells and antigens which will increase the production of antibodies against antigens exposed to the surface of apoptotic cells. The antigen causes T cell and B cell stimulation which contributes to the incomplete clearance of apoptotic cells. During the process of apoptosis, there are pieces of cellular material that form on the surface of the dead cells. Normally, the antigen is not present on the cell surface, but in SLE, the antigen is found on the cell surface. All pathways in SLE lead to endogenous nucleic acid-mediated interferon (IFN-α) production. Increased production of autoantigens during apoptosis (spontaneous or induced by UV light), decreased clearance and deregulation

play important roles in the initiation of autoimmune responses. Nucleosomes contain harmful endogenous ligands that can bind to pathogen-associated molecular pattern receptors, combining with apoptotic blebs which then activate dendritic cells, B cells then produce IFN and autoantibodies. Cell surface receptors such as BCR and FcRIIa facilitate endocytosis of immune complexes or nucleic acid-containing materials and bind to endosomal receptors of the innate immune system such as TLRs. In SLE disease in the early stages, autoantibodies and immune complexes are not yet formed, there is a process of releasing antimicrobial peptides by damaged tissues such as LL37 and neutrophil extracellular traps. The two products released may be bound to nucleic acids so that they can inhibit their degradation and facilitate their endocytosis and stimulation of TLR-7/9 in the plasmacytoid of dendritic cells. Increased levels of endogenous nucleic acids associated with apoptosis stimulate IFN production and autoimmunity with the breakdown of self-tolerance through activation and maturation of conventional dendritic (myeloid) cells. Immature dendritic cells cause tolerance whereas activated mature dendritic cells cause autoreactivity. The production of autoantibodies by B cells in SLE is controlled by the availability of endogenous antigens and is highly dependent on T cell assistance mediated by cell surface interactions (CD40L/CD40) and cytokines (IL21). Immune complexes containing chromatin stimulate B cells via BCR/TLR cross-linking. SLE disease develops when T lymphocytes are activated by antigens presented by Antigen Presenting Cells (APC) through the Major Histocompatibility Complex (MHC), then these activated T lymphocytes will release cytokines, inflammation and stimulate B cells. Stimulation of B cells and production of immunoglobulin G autoantibodies (IgG) can cause tissue damage. T cells and B cells that are specific for autoantigens will interact and produce autoantibodies.[1, 3] Systemic lupus erythematosus is a systemic disease, where the clinical manifestations of this disease involve almost all organ systems, including:

Table 1: Manifestations of Systemic Lupus Erythematosus based on the organs involved.

Organs involved	Symptom
Constitutional manifestation	Fever, fatigue, lymphadenopathy, malaise, decreased appetite, weight loss.
Musculoskeletal	Joint pain, arthritis, muscle weakness, muscle pain, myositis, osteoporosis, tenosynovitis.
Skin and mucosa	Photosensitivity, malar rash (Butterfly rash), discoid rash, alopecia, oral ulcers, subacute cutaneous lupus erythematosus.
Kidney	Proteinuria, hematuria.
Neuropsychiatry	Seizures, chorea, cognitive impairment, peripheral neuropathy, headache, depression, mood disorders, psychosis, organic brain syndrome.
Lung	Pleurisy, alveolar haemorrhage, chronic pulmonary interstitial disease, airway obstruction
Cor	Pericarditis, myocarditis, cardiomyopathy, cardiac conduction disorders
Blood vessel	Vasculitis, Raynaud's phenomenon
Gastrointestinal	Nausea, vomiting, diarrhea, acute abdominal pain, anorexia, pharyngitis, esophagitis, peptic ulcer, malabsorption, ascites, peritonitis, pancreatitis, gastrointestinal bleeding, motility disorders, liver enzyme abnormalities, hepatomegaly, jaundice
Ocular	Dry eye, keratitis, keratoconjunctivitis sica, episcleritis, optic neuropathy, scleritis, uveitis, retinal vasculitis
Obstetric	Premature delivery, low birth weight, small neonates for gestational age, spontaneous abortion, stillbirth, preeclampsia
Endocrine	Vitamin D deficiency, hyperprolactinemia
Hematologic	Iron deficiency anemia, anemia of chronic disease, autoimmune hemolytic anemia, thrombocytopenia, leukopenia and lymphopenia.

The diagnosis of SLE is based on clinical symptoms and laboratory examination. The SLE classification criteria can help in establishing a diagnosis, there are several criteria and the latest currently isSLE classification criteria from ACR/EULAR 2019.[1, 4] Table 2. SLE ACR/EULAR 2019 classification criteria

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

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Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Management for SLE consists of non-pharmacological and pharmacological management. Non-pharmacological management are education about disease, healthy lifestyle, exercise according to ability, balanced nutrition, avoid smoking, avoid exposure to direct sunlight for those who are sensitive, routine control and regular drug consumption. Pharmacological management is based on the severity of disease activity.4

Table 3: Pharmacological management of SLE

SLE Ringan	SLE Sedang	SLE Berat
Terapi Awal		
• Prednison oral ≤20mg/day ~ 1-2 weekor • Metilprednisolon injection 80-120mg IM/IA and • Hiroksiklorokuin ≤6, 5mg/kgbb/dayor • Metrotreksat 7, 5-15mg/weekor • OAINS	• Prednison ≤0, 5mg/kgbb/daywith or without metilprednisoloninjection ≤ 250mg IV/day ~ 3 dayand • Azatioprin 1, 5-2, 0 mg/kgbb/dayor • Metrotreksat 10-25mg/week • or • Mofetil mikofenolat 2-3g/day • or • Asam mikofen0lat 1, 44-2, 16 g/dayor • Siklosporin ≤ 2, 0mg/kgbb/dayand • Hiroksiklorokuin ≤6, 5mg/kgbb/day	• Prednison ≤0, 5mg/kgbb/dayand • metilprednisoloninjection 500-750mg IV/day ~ 3 dayor • Prednisolon ≤0, 75-1mg/kgbb/dayand • Azatioprin 2-3 mg/kgbb/day or • Mofetil mikofenolat 2-3 g/day or • Asammikofenolat 1, 44-2, 16 g/dayor • Siklosporin ≤ 2, 5 mg/kgbb/dayor • Sikofosfamid IV and • Hiroksiklorokuin ≤6, 5mg/kgbb/day

TB is an infectious disease caused by the bacteria Mycobacterium tuberculosis. Extrapulmonary TB is a TB case involving organs outside the lung parenchyma such as the pleura, lymph nodes, abdomen, genitorurinary tract, skin, joints and bones, and the lining of the brain. Tuberculous pleurisy is one of the most common manifestations of extrapulmonary TB, TB pleurisy occurs due to infection with Myobacterium tuberculosis (MTB) in the pleura. The pathogenesis of tuberculous pleurisy results from TB antigen entering the pleural space, usually through rupture of the subpleural foci and interaction with lymphocytes that results in a delayed-type hypersensitivity reaction. Lymphocytes will release lymphokines which will cause an increase in the permeability of the pleural capillaries to proteins that will produce pleural fluid. Type 1 helper T cells (Th 1) subset mediate lymphocytes in responding to MTB infection. This pleural effusion can occur after primary infection or reactivation of TB which may occur if the patient has low immunity and also does not involve bacilli that enter the pleural cavity. The most common clinical symptoms of tuberculous pleurisy are cough, chest pain and fever. Other TB symptoms such as weight loss, malaise, night sweats may occur. The size of the pleural effusion is usually small to moderate and unilateral, may be loculated in one third of cases. The diagnosis of tuberculous pleurisy is based on the presence of tuberculous bacilli in the pleural fluid, a pleural biopsy or granulomas in the pleura on histopathological examination. Conventional methods such as direct pleural fluid examination, pleural fluid culture and pleural biopsy have been shown to be effective in establishing tuberculous pleurisy. Pleural fluid analysis is an easy examination to perform as one of the supporting examinations for the diagnosis of TB pleurisy. The diagnosis of tuberculous pleurisy can use the activity of adenosine deaminase (ADA), pleural fluid proteins, lactate dehydrogenase and cellular components. The ADA value is increased in tuberculous pleural effusions. The ADA examination is a simple, rapid, non-invasive and relatively inexpensive examination, so it must be included in routine examinations in the laboratory. Treatment of pleural TB is the same as the treatment of pulmonary TB with the 2RHZE/4RH alloy. Evacuate fluids as optimally as possible according to the patient's condition.[5, 6, 7]

In our case, a 26-year-old woman came with complaints of shortness of breath, fever, body aches, malaise, mouth sores, hair loss and weight loss. Physical examination revealed oral ulcers, on the back and hands there were papules, erythematous plaques, multiple. On examination ANA (IF) obtained results>1: 1000. So that based on gender, age, patient complaints and physical examination, the patient is suspected of having SLE, then with the results of the patient's ANA (IF) > 1: 1000, the patient can be included in the ACR/EULAR2019SLE classification criteria. With the ACR/EULAR2019SLE classification criteria, the patient got a score of 23 (fever, thrombocytopenia, oral ulcers, cutaneous lupus, pleural effusion, joint involvement), so that with the fulfillment of the ACR/EULAR 2019 criteria (1 clinical criteria and 10 points) the patient was diagnosed with SLE. The Indonesian Rheumatology Association generally distinguishes the determination of the degree of SLE (non-renal) activity based on clinical manifestations and the SLEDAI / MEX-SLEDAI score. The patient in this case had moderate symptoms (pleurisy) and had an SLEDAI score of 8 so that the patient was included in the category of Moderate SLE. The patient was given therapeutic management according to the guidelines of the Indonesian Rheumatology Association (2019) and showed a good response. Furthermore, the patient was suspected of having TB pleurisy because from the anamnesis there were complaints that were suspected as symptoms of TB pleurisy, namely cough, chest pain and fever. In addition, the patient also complained of weight loss and malaise. Physical examination on thorax examination, auscultation at the apex of the left lung found decreased vesicular lung sounds and rhonchi sounds on both sides of the patient's lungs. Supportive examination is from chest x-ray and ADA examination. The chest X-ray revealed a right pleural effusion, then the ADA examination revealed 68.23 U/L. From the anamnesis, physical examination and supporting examination, the patient was diagnosed with TB pleurisy. The patient has been given therapy according to the disease, namely by giving OAT 4FDC 1x3 tab (po) and optimal fluid evacuation has been carried out.

TB infection has a higher chance of infecting someone who is immunosuppressed or as a result of immunosuppressive therapy. In several studies from various countries, data showed that SLE patients had an increased susceptibility to TB infection, especially in areas where TB infection was endemic. In SLE patients, extrapulmonary TB infection is more common than pulmonary TB. In one study, in 3000 SLE patients, 47.6% had pulmonary TB disease while 52.4% had extrapulmonary TB. Patients with SLE are more susceptible to the risk of spread. In a previous study it was found that in TB patients, half of the patients were found to

have TB after being diagnosed with SLE. Erdozain et al. reported a 6-fold higher incidence of TB in the SLE group compared to the general population. Similarly, Mok et al. reported a 5 to 15-fold higher risk. The cellular immune response is involved in controlling TB infection. Impaired cellular and humoral immune function in SLE patients have been shown to be associated with the development of clinical manifestations of TB.[10, 11]

4. Summary

We report a case of a 26-year-old woman with a diagnosis of moderate SLE accompanied by TB pleurisy. SLE is a multisystem autoimmune disease in which organs, tissues and cells are damaged mediated by tissue-binding autoantibodies and immune complexes. The diagnosis is made based on clinical symptoms, then an antibody titer is obtained which after the titer exceeds normal, it can be continued to enter the ACR/EULAR 2019 SLE classification, where the patient's score meets the SLE diagnosis. The diagnosis of TB pleurisy is based on clinical symptoms and examination of the pleural fluid (ADA Test). The main cause of the high incidence of SLE with TB infection is impaired immunity in SLE patients themselves or it could be the result of immunosuppressive therapy.

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