Acute Lupus Pneumonitis with Cytomegalovirus Co-infection in Patients with Lupus Nephritis

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Introduction: Most patients with systemic lupus erythematosus (SLE) show signs of pulmonary involvement. The clinical manifestations of Lupus Pneumonitis are the similar to those of acute interstitial pneumonia. The use of cyclophosphamide in lupus nephritis (LN) is associated with high CMV titers. Ganciclovir is the main choice of therapy for CMV pneumonia infection. Case presentation: A 19-year-old female with previous history of lupus nephritis presented with worsening dyspnea, productive cough with yellowish sputum and hemoptysis. Following physical, laboratory and radiological examinations, the patient was diagnosed with acute lupus pneumonitis, with a differential diagnosis of pneumonia infection. During treatment in the intensive care unit (ICU), she was put on ventilator and received routine hemodialysis due to pulmonary edema. She was given intravenous antibiotics before the culture results came out, but there was no clinical improvement. Once the culture results returned negative, the antibiotics were discontinued and IV pulse methylprednisolone was started. There was significant clinical, radiological, and laboratory improvements. After discharge, the patient experienced hemoptysis again due to CMV pneumonia infection and was given ganciclovir therapy with satisfactory results. Conclusion: In patients with advanced LN and pulmonary involvement, distinguishing between infection and SLE flares may be challenging, which can cause dilemma in diagnosis and treatment decisions. Adequate oxygenation with ventilator, hemodialysis, and administration of ganciclovir and mycophenolic acid provides significant improvements in patient care.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with its relapse-remitting characteristic and autoantibody production in several organs, leading to cell and tissue destruction through antigen-antibody immune complexes.¹

Pulmonary manifestations are documented in several SLE patients, affecting the lungs, pulmonary vessels, pleura, and/or diaphragm.² Pleuritis, cough, or shortness of breath may be the initial signs of either lung involvement or SLE progression.³ However, most pulmonary manifestations in SLE are difficult to distinguish because of their similar characteristics.

Patients with lung involvement should be screened regularly for infections, specifically bacterial or viral pathogens. SLE patients are considered immunocompromised because of the nature of its disease and the current immunosuppressive treatments they acquired.⁴ Opportunistic infections (mycobacteria, fungi, or virus) must be considered thoroughly. Due to the current pandemic, screening for coronavirus is also mandatory as coronavirus pneumatic infiltrates can mimic lupus pneumonitis.⁵

Lung tuberculosis should be considered in the differential diagnosis as it might resemble lupus pneumonitis, especially in countries like Indonesia where tuberculosis is endemic.⁶ Additionally, it is important to rule out non-infectious etiologies such cardiogenic pulmonary edema and drug-induced pneumonitis. Drug-induced pneumonitis should be considered in SLE patients with worsening respiratory...
status, with cyclophosphamide and methotrexate being the most common immunosuppressive medications in SLE associated with this condition. This report presents a case of an SLE patient with pulmonary manifestations indicative of acute pneumonitis, with concomitant cytomegalovirus infection.

2. Case Presentation

A 19-year-old female presented with a chief complaint of worsening dyspnea over the past two days, particularly in the last 6 hours. Her shortness of breath was exacerbated by mild activities. It worsened when lying down and was relieved when she was in a semi-upright position. She had a productive cough with yellowish sputum for the past month and experienced hemoptysis with a volume of up to 100 cc. Over the same period, she suffered from fatigue for 2 weeks, which worsened a day before she came to the emergency ward.

The patient was diagnosed with SLE two and a half years ago (October 2020) with initial complaints of knee pain, maculopapular rash on the trunk, hair loss and intermittent fever. She also had history of foamy urine accompanied by generalized swelling 2 years ago. A renal biopsy performed in January 2023 showed mesangial proliferation and was concluded as lupus nephritis class II. She had been on hydroxychloroquine 300 mg once daily, mycophenolate sodium 2x360 mg for the last 9 months, calcium carbonate 2x500 mg per day, isosorbid dinitrate 3x5 mg per day, lansoprazole 30 mg once daily, furosemid 3x40 mg per day, ramipril 10 mg once daily, and N-acetylcysteine 3x200 mg per day.

On physical examination, patient appeared severely ill and dyspneic, but still maintained consciousness (Compos Mentis). Her initial blood pressure was 212/138 mmHg, indicating a hypertensive crisis, with tachycardia, tachypnea, and an oxygen saturation of 87% on room air, which increased to 99% after receiving 15 litres per minute of oxygen by mechanical ventilation. Neck exam showed jugular vein distention (R±5 cm H₂O). Chest examination showed decreased vesicular sounds in the basal left lung. Fine rales were heard in medial and basal lung fields bilaterally. On cardiac examination, there was an audible diastolic murmur of grade III/VI with medium pitch was heard parallel to mitral valve projection. Bilateral pretibial pitting edema was also noted.

Her laboratory results indicated normochromic normocytic anemia (Hb 7.2 gr/dl), leukocytosis (28,320/µl), elevated transaminase enzymes (AST 52 U/L and ALT 453 U/L), procalcitonin (8.99 mg/dl), creatinine (3.25 mg/dl) and urea serum level (144.8 mg/dl), with low eGFR (19 ml/minutes/1.73 m²). Severe hyponatremia with normal osmolarity was also noted (125 mmol/L). Complement blood test showed low levels of C3 and C4, high anti ds-DNA levels (>200), and anti-cardiolipin levels were within normal limit. Blood gas analysis showed fully compensated metabolic acidosis with severe acute respiratory distress syndrome (ARDS). Chest X-ray imaging revealed marked alveolar type pulmonary edema with pneumonia. Echocardiography was performed with the following results: low ejection fraction of left ventricle (Biplane LVEF 39%), mild tricuspid regurgitation with high probability of pulmonal hypertension, and mild-moderate pericardial effusion without chamber collapse.

Patient was admitted to intensive care unit (ICU) and placed on a ventilator. Emergency hemodialysis was conducted afterward due to acute pulmonary edema, followed by nicardipine infuse pump for hypertensive emergency management. She was also administered with IV ceftriaxone 2 grams/day, as suspicion of infections could not be excluded, while waiting for culture results. Other medications included intravenous furosemide 10mg/hour, oral ramipril 5 mg per day, bisoprolol 2.5 mg per day, ISDN 5 mg twice a day and N-acetylcysteine 200 mg three times a day. Blood, sputum, and urine culture showed bacterial growth. The Candida colonization index scored <0.5, indicating no invasive candidiasis. After seven days of antibiotics and intermittent hemodialysis, the shortness of breath had not subsided. High-Resolution CT scan (HRCT) was
performed, which showed bilateral ground glass opacity, supporting the diagnosis of acute lupus pneumonitis. Ceftriaxone was discontinued after seven days, and intravenous pulse dose of methylprednisolone (500mg/day for 3 days) was given, followed by tapered dose of oral methylprednisolone and re-initiation of mycophenolic acid 720mg twice daily. Subsequently, there was significant improvement, as shown by clinical, radiological, and laboratory findings (shown in Figure 1).

The patient was discharged after 17 days of admission. During outpatient evaluations, she experienced cough followed by persistent hemoptysis. Since previous tests did not find any bacterial and fungal infections, serological testing for IgM/IgG CMV was performed, and both showed elevated levels of 1,611>500 U/mL. The clinician decided to start valganciclovir 900 mg twice a day for 21 days as an induction dose, followed by 900 mg once daily for 3-6 weeks as a maintenance dose. The patient has since returned for follow-up appointments with significant improvement.

![Graphical Timeline of the Progressivity of Patients Conditions and Treatment](image)

**Figure 1.** Graphical Timeline of the Progressivity of Patients Conditions and Treatment

### 3. Discussion

Pulmonary involvement in SLE patients is common, but the prevalence of lupus pneumonitis is still rare (<5%). Clinical manifestations of lupus pneumonitis are similar to acute interstitial pneumonia, which is a subtype of idiopathic pneumonia. Signs and symptoms may appear acutely and insidiously, such as fever, hemoptysis, and shortness of breath. Physical examination may reveal tachypnoea, tachycardia, basilar inspiratory crackles, and hypoxemia. Laboratory investigations include complete blood count with cytopenia, increased level of anti-dsDNA, and increased levels of brain-natriuretic peptide (NT-proBNP) can help exclude cardiogenic cause. Screening for opportunistic infections by virus pathogens, serological testing for atypical pneumonia (*Coccidioides, Chlamydia pneumoniae, Mycoplasma pneumoniae, respiratory viruses*) and opportunistic pneumonia (*Aspergillus, Candida, Cryptococcus, and Pneumocystis jirovecii*)
could also be conducted.\textsuperscript{9}

Imaging workup, such as HRCT of the lung, shows a ground-glass appearance, which apart from being useful for diagnosis, it can also be used to exclude suspicions of pulmonary embolism or antiphospholipid syndrome. Other investigations such as the diffusing capacity for carbon monoxide (DLCO) and bronchoalveolar lavage (BAL) can help to differentiate lupus pneumonitis from diffuse alveolar hemorrhage. Biopsy can also be performed, with alveolar damage, alveolar oedema, hyaline membrane formation, mononuclear cell infiltration, and deposition of immune complexes in the vascular wall as histopathological findings.\textsuperscript{10}

Lupus nephritis (LN) is one of the fatal manifestations of SLE, which usually appears after five years of diagnosis. The presence of LN is confirmed through histological examination of the kidney. Symptoms of LN ranges from proteinuria, hypertension, to kidney failure. Kidney biopsy is recommended for every SLE patient with nephritis symptoms or impaired kidney function which lead to nephritis.\textsuperscript{11}

Pharmacological therapy is adjusted based on LN degree. LN class I-II generally does not require immunosuppressive therapy, while class III/IV requires glucocorticoid and immunosuppressive therapy. Induction therapy for class III/IV LN includes mycophenolate mofetil (MMF) (2-3g total daily dose orally) or intravenous cyclophosphamide (CYC) with glucocorticoids. LN class V (subepithelial immune deposits and thickening of the glomerular capillary membrane), with class III or IV combination, can be treated similarly to class III or IV LN. LN class VI (sclerosis of $>90\%$ of glomeruli) requires preparation for renal replacement therapy rather than immunosuppressants.\textsuperscript{11}

In this patient’s case, the presentation of severe acute lung edema followed by ARDS was suspected as Rapid Progressive Glomerulonephritis, and IV pulse dose of methylprednisolone was urgently needed. However, the increased leukocyte and procalcitonin posed a dilemma at whether to start high dose steroid or treat the potential infections.

Cytomegalovirus (CMV) infection, the most common human infection worldwide, is usually asymptomatic. Development of CMV modern diagnostic methods support that CMV is the most common opportunistic infection found in fetus, allograft recipients, patients receiving bone marrow transplants, and rheumatology patients on long-term immunosuppressive treatment. These conditions may lead to systemic reactivation, leading to systemic organ failure. Risk factor for CMV pneumonia is related to higher dose of steroid use, including immunosuppressive doses. In SLE, a history of cyclophosphamide use in LN is associated with higher CMV titer and bone marrow suppression which manifests as lymphopenia. A study from Fujimoto (2013) also stated that lymphopenia <700 mm$^3$ could be a risk factor for CMV infection.\textsuperscript{12}

CMV infection can trigger macrophage activation syndrome, therefore, ganciclovir therapy plays a key role in the management. However, ganciclovir administration has several risk of side effects, such as myelosuppression, infertility, and potential worsening of liver and kidney function. In a study from Takizawa (2013), ganciclovir was recommended for CMV pneumonia infection accompanied by diffuse parenchymal lung disease, which was clinically and supportively described in patients.\textsuperscript{12}

4. Conclusion

Most patients with SLE show signs of involvement of lungs, pulmonary vasculature, pleura, and/or diaphragm. Pleurisy, cough, and/or dyspnea often precede either pulmonary involvement or SLE progression. Screening of infection for suspected host infection is crucial. Lupus pneumonitis presents clinical features similar to interstitial pneumonia, thus imaging workup with HRCT is needed to support the diagnosis. Reactivation of CMV infection might be related to the dose and duration of immunosuppressive agents. In LN patients of advanced severity, including pulmonary involvement, it is quite difficult to decide whether the symptoms are
due to infections or SLE flares, which can cause a dilemma in diagnosis and therapy decisions. Adequate oxygenation with ventilator, hemodialysis, and ganciclovir and mycophenolic acid administration have shown significant improvements in patient care.

5. References