



Covid-19 in Lupus Nephritis

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ABSTRACT

COVID-19 outbreak is currently being concerned for managing patients with immunological disorders nowadays, including SLE. Lupus is a complex autoimmune disease characterized by the presence of autoantibodies that against cell nucleus involved many organs in the body. Patients with SLE will increase risk of severe infection because the intrinsic respond attack with their immune respond though immunosuppressive drugs consumption, and will potentially damage some organs target associated with their disease. Lupus have multiple clinical manifestations with a fluctuating symptom. Patient who come with the symptom of breathlessness will get worse day by day. The symptom could be felt in the same time as fatigue, joint pain, hair loss, malar rash, oral ulcer, pleural effusion and swollen feet. There's a patient with antinuclear antibody positive for anti-smith and anti-Ro/SS-A. She was diagnosed with COVID-19, SLE with nephritis, haemolytic anemia, vasculitis and pleural effusions. The clinical manifestations of this patient indicate a COVID-19 with lupus nephritis that has severe disease. She was being treated with methylprednisolone and hydroxychloroquine for SLE and azithromycin plus oseltamivir as a therapy for COVID-19. The effect of hydroxychloroquine on SARS-CoV-2 was better seen in patients with SLE who got the medication regularly. Patients went home after 24 days of hospitalization after negative RT-PCR results and clinical improvement of LES.

1. Introduction

In December 2019, pneumonia as the new corona virus spread in Wuhan, China. This study on patients with pneumonia revealed that a previously unknown type of beta-coronavirus that is similar to the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The causative agent is named SARS-CoV-2 by the Coronavirus Group, and the disease it caused by Coronavirus Disease 2019 (COVID-19) from the World Health Organization (WHO). Coronavirus is characterized in different virus, enveloped, positive-sense, single-chain ribonucleic acid (RNA) viruses that belong to two subfamilies, Coronavirinae and

Torovirinae, in the Coronaviridae family.^{1,2}

Eventhough lot of coronavirus infections only cause mild respiratory symptoms, infections with SARS-CoV, MERS-CoV, and SARS-CoV-2 could be falling in death condition. COVID-19 infection can carry different clinical manifestations, from mild to severe clinical with acute respiratory disease syndrome (ARDS), sepsis and shock, multi-organ failure and even death. Severe clinical COVID-19, which occur in 5% of cases that results in hypoxemic respiratory failure which is well-known to be the result of uncontrolled inflammation coupled with a reduced and dysfunctional lymphocyte response.^{2,3}

The COVID-19 outbreak is currently one of

particular concern for managing patients with immunological disorders including systemic lupus erythematosus (SLE). Systemic lupus erythematosus is a complex autoimmune disease characterized by the presence of autoantibodies against the cell nucleus that involves many organs in the body. Genetic predisposition, environmental factors, and hormonal environment will promote the disease and each other in disease development and activity. The clinical manifestations and related of organ involvement are highly heterogeneous, reflecting the complex mosaic of disrupted molecular pathways that coalesce with the clinical phenotype of SLE. Lupus has various clinical manifestations on the skin, joints, kidneys and other organ systems which do not coexist, but may develop as the disease progresses. Fluctuating course of lupus, experiencing exacerbations and remissions.^{4,5}

Patients with SLE have an increased risk of severe infection because of intrinsic interference with their immune response, use of immunosuppressive drugs, and the potential for organ damage associated with their disease. This disease is often treated with hydroxychloroquine or chloroquine, both of which are also used in the treatment of COVID-19. Lupus has always had unique challenges in its diagnosis and management, even in the midst of the current COVID-19 pandemic. It remains unclear at this point whether patients with SLE have an increased risk of contracting COVID-19 or if there is a paradoxical protective effect due to the use of hydroxychloroquine. Debate continues over the role of hydroxychloroquine in the management of COVID-19, with increasing data that do not confirm the protective effect of this drug against SARS CoV-2 in general and also in patients with SLE in particular.^{3,6,7}

Patients with SLE have the same risk as the general population for contracting COVID-19 but with no better clinical manifestations. According to Global Rheumatology Alliance data, patients with SLE who suffer from COVID-19 account for 17%. In the research conducted by Mathian et al. in 17 SLE patients with COVID-19, 7 (35%) were of a severe disease requiring mechanical ventilation assistance or extracorporeal membrane oxygenation.^{4,8,9}

Cassione et al. who conducted a study on 165 patients with SLE, 12 patients (7.2%) were confirmed COVID-19 with symptoms including fever, breathlessness, cough and anosmia plus direct contact with previous COVID-19 confirmed patients. Among these patients, 10 (83%) used hydroxychloroquine, 4 (25%) used glucocorticoids, 6 (50%) mycophenolic acid (MPA) / mycophenolate mofetil (MMF) and 1 patient (8.3%) used other immunosuppressants. According to Gartshteyn et al. who reported 18 cases of SLE with COVID-19 in New York, 15 (83%) on immunosuppressants, 7 (39%) on steroids, 13 (72%) hydroxychloroquine or chloroquine, with 11 (61%) having lupus nephritis.^{3,10}

Clinical findings

A 32-year-old female patient as a housewives, get hospitalized in isolation ward with symptom breathlessness that was getting worse since one day ago. The symptom felt in one week. Patient also felt of painful in joint since one week ago which comes in the fingers and then felt throughout the body. Since two months ago, patient complained of frequent hair loss and mouth ulcers. Red spots also appeared on her's face since one month ago, these spots were especially visible after exposed to sunlight. Since the past two weeks she had also complained about his swollen legs and frequently frothy urination. She often feels weak, tired and looks pale. Patient also had a history of pregnancy four times with two miscarriages. She had no other previous illnesses and family history with the same complaints.

From the physical examination, it was found that the condition was moderate with a blood pressure of 150/90 mmHg and a respiratory rate of 26 times per minute. Overall, she had edema, alopecia, malar rash on the face, oral trash in the mouth, and anemic conjunctiva. From physical examination of the lungs, it was found that fremitus was decreased, percussion was dim and the sound of breath was decreased in the basal both of lungs. The physical examination of the abdomen revealed ascites. On laboratory tests, hemoglobin was found 9.2 gr/dl, leukocytes

10460/mm³, platelets 498.000/mm³, albumin 1.2 gr/dl, urea 8.5 mg/dl, creatinine 2.1 mg/dl, potassium 2.7 mmol/dl, d-dimer > 10.000 ng/ml, total cholesterol 386 mg/dl, HDL 45 mg/dl, LDL 261 mg/dl and triglycerides 401 mg/dl. The patient's urinalysis showed protein 1-2 gram/day, with urinary leucocytes and erythrocytes. Patients also had a coomb's test with a positive direct coomb's test result. Chest x-ray examination of the patient revealed bronchopneumonia with minimal bilateral pleural effusions. She was checked for nasopharyngeal swab and examined for reverse transcription-polymerase chain reaction (RT-PCR) with a positive result. To trace the diagnosis of lupus, she was examined for immunological marker profiles with a positive anti-smith and anti-Ro/SS-A result.

Patient was diagnosed with COVID-19, SLE with nephritis, haemolytic anemia, vasculitis and bilateral pleural effusions. For COVID-19 patients were treated with the antiviral oseltamivir 150 mg/day for five days, azithromycin 500 mg/day, zinc 20 mg/day, vitamin C 500 mg/day, n-acetyl cysteine 600 mg/day and heparin 15.000 IU/day. For SLE, methylprednisolone 48 mg/day and hydroxychloroquine 200 mg/day were given with support for amlodipine 5 mg/day, candesartan 8 mg/day, simvastatin 40 mg/day, furosemide 80 mg/day and folic acid 5 mg/day. She was also given intravenous albumin therapy because of the severe hypoalbumin condition and a blood transfusion to correct her anemia.

Patients went home after 24 days of hospitalization after negative RT-PCR results and clinical improvement of SLE. She went home with methylprednisolone 32 mg/day, hydroxychloroquine 200 mg/day, candesartan 8 mg/day, simvastatin 40 mg/day, furosemide 40 mg/day and folic acid 5 mg/day.

2. Discussion

The COVID-19 outbreak is currently of particular concern for managing patients with immunological disorders, including SLE. Lupus is a complex autoimmune disease characterized by the presence of autoantibodies against the cell nucleus that involves

many organs in the body. Lupus has various clinical manifestations on the skin, joints, kidneys and other organ systems which do not coexist, but can develop with the course of the disease. Patients with lupus have the same risk as the general population for contracting COVID-19 but with no better clinical manifestations.^{4,5}

The clinical manifestations and investigations of this patient indicated a COVID-19 occur in SLE with lupus nephritis. There are complaints of joint pain, frequent hair loss, recurrent mouth sores, reddish spots on the face, especially after exposure to sunlight, weakness, fatigue, swollen feet and frequently frothy urination. Physical examination found malar rash on her's face, mouth ulcers and serositis in the form of pleural effusion. From the laboratory test, she had anemia, the urinalysis revealed proteinuria, hematuria and leukocyturia. Antinuclear antibody test was positive for anti-smith and anti-Ro/SS-A. Immunological marker tests is an important step in diagnosing SLE, including in patients with COVID-19. According to Zhou et al., Anti-Ro/SS-A is the immunological marker most often found in SLE patients with COVID-19. Where from a total of 20 patients, there were nine patients who had antibody Ro/SS-A.¹¹

Based on the criteria for Systemic Lupus International Collaborating Clinics (SLICC), the diagnosis of SLE is at least four out of 17 criteria within clinical criteria and one immunological criteria. These patients met nine of the 17 criteria for the diagnosis of SLE. The SLICC criteria issued in 2012 had a sensitivity of 97% and a specificity of 90% for diagnosing an SLE. Meanwhile, according to the criteria of the American College of Rheumatology (ACR) 2019, the diagnosis of SLE can be made at least four of the 11 criteria are found. In this patient, based on the ACR criteria, met eight of the 11 criteria for an SLE. The 2019 ACR criteria have better sensitivity and specificity than the 2012 SLICC in diagnosing an SLE, namely 98% and 96%, respectively.¹²

Lupus nephritis is defined as clinical and laboratory manifestations that meet the ACR criteria, namely proteinuria > 0.5 g / 24 hours or positive three on dipstick, and/or cellular cylinders including

erythrocytes, granular, tubular or combination of them. Kidney biopsy should be performed in patients with renal involvement because clinical and laboratory parameters cannot provide accurate histopathological features. However, a kidney biopsy was not performed in the patient because the COVID-19 condition in the patient did not allow a diagnostic biopsy to be performed. This patient was classified in class III lupus nephritis according to WHO criteria. This classification is intended to facilitate the determination of therapy.^{12,13}

In general, patients with autoimmune diseases with high disease activity are more at risk of developing any kind of infection, be it viral or bacterial. Therapies received by patients such as immunosuppressants and corticosteroids also contribute to an increased risk of infection or worsen the patient's condition if exposed to an infection such as COVID-19. According to data from the Global Rheumatology Alliance, 17% of patients with LES who suffer from COVID-19 make up. Meanwhile, in the research conducted by Mathian et al. in 17 LES patients with COVID-19, 7 (35%) required assistance with mechanical ventilation or extracorporeal membrane oxygenation.^{4,8,9}

LES disease activity assessment is needed to determine the suitability of the therapy plan for each individual because therapy in these patients is tailored to the disease activity. These patients based on the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI-2K) have LES serious disease activity. According to KDIGO, class III lupus nephritis, with or without a membrane component, is initially treated with corticosteroids plus low-dose intravenous cyclophosphamide or MPA. Meanwhile, according to the ACR, induction therapy includes MPA/MMF and intravenous pulse methylprednisolone. Treatment options for COVID-19 are currently supportive infection control measures and complication management. It is generally recommended to avoid corticosteroids especially in mild symptoms because they may result in prolonged viral replication. However, there are currently no official guidelines on delaying administering immunosuppressants to patients with autoimmune

disease with COVID-19. So that for LES therapy, the patient is only given oral methylprednisolone therapy 48 mg / day and hydroxychloroquine 200 mg / day.^{7,13,14}

According to Cassione et al. who conducted a study on 165 patients with LES, 12 people (7.2%) were confirmed COVID-19 with symptoms including fever, breathlessness, cough and anosmia, direct contact with previous COVID-19 patients. Among these 12 patients, 10 patients (83%) used hydroxychloroquine, 4 (25%) used glucocorticoids, 6 (50%) MPA / MMF and 1 (8.3%) used other immunosuppressants. According to Gartshteyn et al. who reported 18 cases of LES with COVID-19 in New York, 15 (83%) used immunosuppressants, 7 (39%) used steroids, 13 (72%) used hydroxychloroquine or chloroquine, with 11 (61%) having lupus nephritis.¹⁰

Viral effects and immune system-mediated mechanisms are two of the main causes of severe clinical events in LES patients with COVID-19. Based on the severity of the case, this patient was classified as moderate because the patient had clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no sign of severe pneumonia, SpO₂ ≥ 93%. According to the COVID-19 Management Guidelines compiled by five professional organizations in Indonesia, moderate COVID-19 patients should be given pharmacological management of azithromycin 500 mg / day plus one of the antiviral favipiravir or remdesivir and vitamin C 600-1200 mg / day, as well as administration anticoagulants and other symptomatic medications. In patients given the antiviral oseltamivir 150 mg / day due to impaired renal function in patients, according to Roberto et al., The use of remdesivir and favipavir must be careful in their use in patients with renal impairment.^{11,15,16}

The course of LES is generally mild and self-limiting, although a severe course may occur. Interestingly, COVID-19 occurs despite a long history of hydroxychloroquine therapy. The role of hydroxychloroquine in COVID-19 is still being debated. Although there is no data to suggest that hydroxychloroquine can provide protection against infection, no conclusions can be drawn from this, as

the concurrent use of other immunosuppressive therapies can affect the incidence and course of COVID-19.¹⁰

Antimalarials are important drugs in the treatment of LES because they modulate antigen internalization and processing by phagocytes in addition to their antimicrobial and cardioprotective effects. However, several weeks of accumulation of this drug into the body is required before observing a clinically relevant effect. Based on this evidence, it has been hypothesized that the prophylactic effect of hydroxychloroquine on SARS-CoV-2 is better seen in patients with LES who are taking it routinely (although usually at a lower dose), than in the acute phase of COVID-19.⁶

According to Ramirez et al, in vitro data suggest that antimalarials, including hydroxychloroquine can reduce the virulence of SARS-CoV-2, by reducing endosomal pH and possibly affecting post-transcription editing of angiotensin converting enzyme 2, a viral receptor on target cells, but in vivo evidence is currently controversial and randomized controlled trials are ongoing. Konig et al. identified 80 patients with LES and COVID-19 and concluded that patients with LES on baseline therapy with hydroxychloroquine were not completely protected from COVID-19. Patients were dominated by women and aged less than 65 years, with the same proportion in the degree of symptoms of COVID19.^{6,17}

3. Conclusion

The increasing incidence of COVID-19 makes us should be aware from this disease. It is also affected in patients with immunocompromise such as in SLE patients. Optimal management, not only SLE, but also COVID-19 management, frequently in symptomatic patients, must be achieved to maintain the survival of SLE patients.

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