Severe COVID-19 Infection in a Lupus Nephritis Patient on Treatment for Multidrug-Resistant Disseminated Tuberculosis

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Abstract

Background: Systemic lupus erythematosus is a multisystem autoimmune disease with variable manifestations, dysregulated type I interferon responses, and defective immune tolerance mechanisms. SLE, multidrug-resistant tuberculosis (MDR-TB), and coronavirus disease 2019 infection may be a rare, complex combination presenting a significant challenge in screening, management, and infection control.

Case: A 24-year-old female diagnosed with SLE nephritis maintained on mycophenolate, mofetil, and hydroxychloroquine developed disseminated multidrug-resistant tuberculosis (MDR-TB) involving the lungs, liver, and lymph nodes. She was started on an anti-TB regimen. However, QT prolongation and heart failure was noted, thus discontinuation of HCQ. On the 10th month of treatment with clofazimine, cycloserine, p-aminosalicylic acid, and delamanid, she developed fever, dyspnea, chest pain, and disorientation accompanied by progressive oxygen desaturation. A nasopharyngeal swab for SARS-CoV-2 RT-PCR was positive, and a high-resolution chest CT showed new peripheral ground-glass opacities consistent with COVID-19 pneumonia. Oxygen support with a high-flow nasal cannula at 60% FiO2, low molecular weight heparin, meropenem, remdesivir, and dexamethasone were given; MDR-TB treatment was temporarily withheld. The patient recovered after 3 weeks of hospitalization, and MDR-TB treatment was resumed following hospital discharge.

Conclusion: This case illustrates the challenges in healthcare access brought about by the pandemic and the management of drug-to-drug interactions in the different treatment regimens for lupus nephritis, disseminated MDRTB, and severe COVID-19 infection.

Keywords: severe covid-19 infection, lupus nephritis, multi-drug resistant tuberculosis, management challenge,

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by its variable manifestations, dysregulated type I IFN responses, and defective immune tolerance mechanisms. Bacterial, viral, and opportunistic infections are common in SLE.[1] These infections contribute to the burden of morbidity and mortality in SLE. SLE has a greater mortality risk, 2.5 times the rate of the general population.[2]

The two main risk factors in the development of infection include using long-term immunosuppressants such as steroids and cyclophosphamide. In addition, impaired immune functions make them susceptible to infections.[3] SLE patients are more likely to develop TB, which is more frequently extrapulmonary, with more extensive pulmonary involvement and a higher relapse rate. Therefore, high mortality figures are expected in developing countries that have detected high incidence of extrapulmonary tuberculosis.

According to the World Health Organization (WHO) report, the Philippines has the highest TB incidence in Asia, with 554 cases per 100,000 people. In addition, it has a high burden of tuberculosis (TB), with an estimated 290,000 new TB cases each year and multidrug-resistant

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TB (MDR-TB). Approximately 74 Filipinos die of TB every day, which is among the country's top 10 causes of death.

Although SLE and MDR-TB may be a rare combination, the increase in the global incidence of MDR-TB may mean that clinicians worldwide will encounter more such cases frequently. It is essential to holistically evaluate the risks and benefits while selecting the treatment components for MDR-TB and SLE.[5]

In early 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), infected millions worldwide. Patients with SLE are unique when considering the risk of contracting COVID-19 and the infection outcomes. The underlying organ damage from SLE and the use of systemic glucocorticoids (sGC) and immunosuppressants could be risk factors for developing severe COVID-19. SLE, MDR-TB, and COVID-19 present subsequent challenges in screening, management, and infection control.

Thus, we report the complicated and challenging case of a lupus nephritis patient on treatment for multidrug-resistant disseminated tuberculosis who developed severe COVID-19 infection.

Case Report

This report is a case of a 24-year-old female patient presenting with prolonged febrile episodes and pericarditis in 2012. Workup for SLE showed: ANA 1:320 (homogenous pattern), low C3, and positive anti-dsDNA. Thus prednisone 40 mg once daily on tapering doses and hydroxychloroquine 200 mg once daily were started. Six years later, she developed proteinuria (3+) and grade II bipedal pitting edema; a kidney biopsy showed nephritis class IV (A/C). Mycophenolate mofetil (MMF) 500 mg twice daily.

In early 2020, she had episodes of fever and productive cough, thus prompting admission. She was started empirically with intravenous piperacillin-tazobactam 4.5 grams every 6 hours, trimethoprim/ sulfamethoxazole 240 mg every 8 hours, fluconazole 200 mg every 24 hours, and oral methylprednisolone 16 mg daily. *Pneumocystis jirovecii* – DNA test turned out negative, thus, TMP/SMX was discontinued. Sputum acid-fast bacilli (AFB) smear, sputum culture, and mycobacterium tuberculosis – polymerase chain reaction (MTB-PCR) showed positive for MTB and resistance to rifampicin (positive *rpoB* gene). Myrin-P forte™ (a combination HRZE tablet) 40mg/ 150mg/ 275mg/ 75mg tablet, three tablets were initially started.

On the 10th day of hospitalization, she complained of right upper quadrant tenderness. A whole abdominal ultrasound showed multiple hypoechoic nodules/complicated cysts in both hepatic lobes. Dynamic liver computed tomography scan showed multiple complicated hepatic and splenic cysts with enlarged necrotic retroperitoneal, periportal, and paraesophageal lymph nodes and noted innumerable nodules in the lung bases, which were indicative of disseminated tuberculosis. Imipenem-cilastatin 500 mg every 6 hours, a third-line anti-TB agent, was added. Prolonged QT was documented on 12-lead ECG, and she developed heart failure with reduced ejection fraction (HFrEF); thus, imipenem-cilastatin and hydroxychloroquine were discontinued. Heart failure medications included furosemide and sacubitril, and valsartan. The sputum sensitivity test revealed further resistance to other first-line drugs, including isoniazid, pyrazinamide, and ethambutol, with only known susceptibility to streptomycin and resistance to ampicillin and benzylpenicillin, thus managed as a case of MDR-TB. She was started on bedaquilline 100 mg 4 tablets 3 x a week, prothionamide 200 mg 2 caps/day, cyclosporine 250 mg 2 caps/day, linezolid 600 mg 1 tab/day, and pyridoxine 50 mg 4 tabs/day. She developed numerous side effects from anti-MDRTB regimens, including headaches, nausea, vomiting, and myalgia. Dexamethasone helped in the symptoms, but bedaquiline was eventually changed to delamanid. During delamanid treatment, she developed occasional dizziness.

While on treatment with anti-MDRTB and battling side effects, the patient experienced fever, sore throat, body malaise, arthralgia, dry cough, nausea and vomiting, decreased appetite, abdominal pain, diarrhea, generalized weakness, disorientation, difficulty of breathing and oxygen desaturation as low as 79%. Access to care during this time was difficult as the hospitals and emergency rooms were filled with patients with COVID-19. As a mitigating measure, she resumed dexamethasone 5mg tablet while awaiting a hospital to accommodate her. There was no improvement in symptoms, and she was accommodated to come to the hospital after 72 hours of waiting at home. At the ED, vital signs showed a BP of 100/70, HR of 121 bpm, respiratory rate of 32 rpm, and temperature 38.6°C. Arterial blood gas showed PaO_2/FIO_2 of 174 mmHg. A nasopharyngeal swab for SARS-CoV-2 RT-PCR test was positive, and HRCT showed peripheral lung ground-glass opacities consistent with COVID-19 pneumonia (see *Figure 1*).

She was managed as a case of severe COVID-19 infection. According to the WHO, patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%. She was placed on high-flow nasal cannula at 60% FiO_2. Intravenous meropenem 1 gram every 8 hours, remdesivir 200 mg once a day, dexamethasone 6 mg every 24 hours, and subcutaneous enoxaparin 40 mg daily were given. Due to numerous side effects and unknown drug-to-drug interactions between remdesivir and the anti-MDRTB regimen, the MDR-TB treatment was withheld temporarily against recommendations to continue, also considering the current heart condition and unknown risks of COVID-19 therapy to the risk of additional morbidity and mortality. Eventually, the patient recovered after three weeks of hospitalization, and MDR-TB treatment was resumed immediately following hospital discharge.

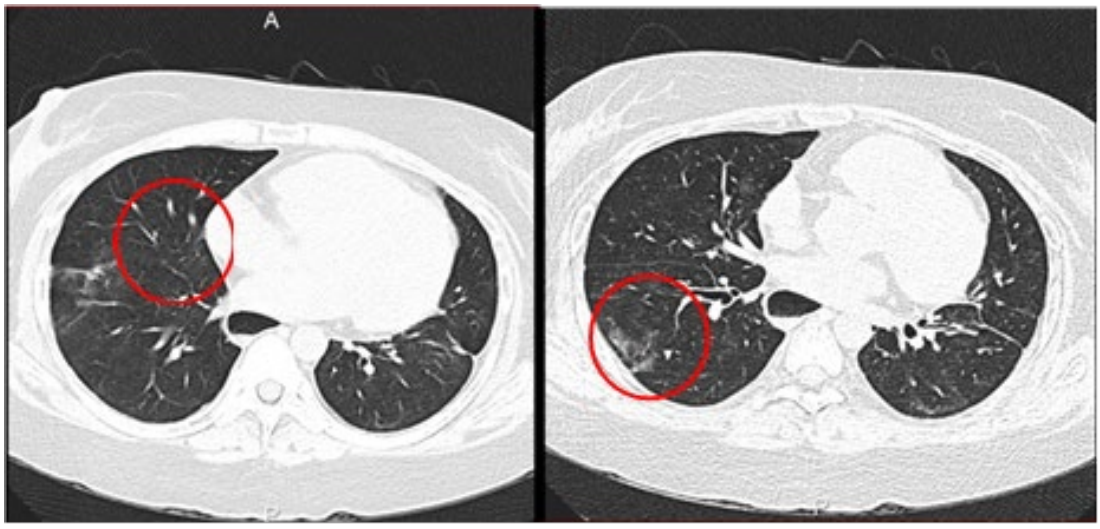

Figure. 1. Peripheral lung ground-glass opacities consistent with COVID-19 pneumonia

Case Discussion

Systemic lupus erythematosus (SLE) is a systemic disease of unknown etiology, characterized by autoantibodies against self-antigens, resulting in inflammation-mediated multiorgan damage. In patients with SLE, there are immunologic and genetic alterations that predispose them to develop infections.[7]

A study by Fernandez-Ruiz et al. noted that complement dysregulation is common in SLE and worsens with disease activity. Infections, renal failure, and cardiovascular diseases account for most SLE patients' deaths.[7] Gram-positive or gram-negative bacteria cause most infections. Interestingly, there is an increase in the incidence of Mycobacterium tuberculosis (MTB) and other opportunistic infections in SLE that also account for increased mortality. [8]

SLE and tuberculosis (TB) interact in complicated ways – they may have similar presentations and mimic each other likelihood of development of TB in lupus patients depending on the local prevalence and incidence of TB. Several mechanisms have been suggested by which microbes may trigger autoimmune reactions. Firstly, microbial antigens may be associated with self-antigens to form immunogenic strains and bypass T-cell tolerance. Secondly, certain bacterial and viral products are non-specific polyclonal B-cell mitogens and may induce the formation of autoantibodies. Thirdly, the infection may cause the suppression of T-cell functions·[12]

Patients with SLE are also at increased risk of dissemination. This may either be due to their disease or to the use of immunosuppressive medications. Our patient initially presented with a history of cough and fever, and further workup revealed MDR-TB. However, ten months after her ongoing treatment with MDR-TB, she had severe COVID-19 pneumonia, making management more complicated. SARS-CoV-2, a single-stranded RNA virus and the causal agent of COVID-19, has infected millions of people worldwide. The virus enters the cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which determines viral tropism. The type 2 transmembrane serine protease is also required to complete the fusion process by cleaving the ACE2 molecules and activating the SARS-CoV-2 S protein.[15]

One interesting feature is that inflammation in SLE is often characterized by elevation of type I interferon (IFN), which has antiviral properties and could potentially be protective. However, this protective mechanism is largely unknown, and even if true, it could be offset by other sociodemographic, biological, and clinical aspects of the disease and its management. In addition, excessive complement activation with consequent development of thrombotic microangiopathy has been identified in many patients with COVID-19 and seems to at least partially mediate organ dysfunction in severe cases, resembling complement-mediated thrombotic microangiopathy.

Although complement consumption is a classic feature of SLE, the classical pathway is often the main target of activation by immune complexes in SLE, whereas the alternative and lectin-based complement pathways seem to play a more significant role in COVID-19 pathogenesis. [16.] Complement activation has been associated with the excessive inflammatory response seen in patients with severe COVID-19, and the presence of a complement-mediated microvascular injury syndrome has been proposed based on the observed pattern of tissue damage.

In managing patients with MDR-TB and COVID-19 pneumonia, the medications carry potential adverse side effects that may be exacerbated by symptoms associated with COVID- 19. Bedaquiline, delamanid, fluoroquinolones, and clofazimine can all cause QTc prolongation. In addition, SARS-CoV-2 infection is associated with cardiac involvement and myocardial inflammation. Therefore, using these anti-TB medications

in COVID-19 patients may induce more severe cardiac manifestations.[17] This conundrum of whether to continue the anti-MDRTB regimen during remdesivir treatment was a challenge as there is a lack of literature looking at the drug-to-drug interaction of remdesivir to the aforementioned anti-MDRTB regimen our patient is receiving and the concomitant heart failure (HFrEF) and previous history of iatrogenic QT prolongation.

Various reports have indicated that COVID-19 infection may worsen SLE manifestations.[19] Attributing SLE flares to a biologic mechanism is challenging because many of these patients have had more difficulty accessing health care during the pandemic and may suffer worsened disease control due to lack of medical care or difficulty continuing their SLE medications, in addition to the psychosocial stressors of the pandemic.[14] During the COVID-19 pandemic, healthcare access was difficult, especially among patients with non-communicable diseases. Moreso, during surges of COVID-19 cases, hospitals are overwhelmed by the sheer number of cases compounded by a lack of medical staff and resources. Our patient experienced this and had to wait at least three days to be accommodated and managed accordingly.

Conclusion

After a comprehensive review of the literature, it is concluded that our case is infrequent and reportable. No literature has been found yet regarding a case of SLE nephritis with disseminated MDR-TB and heart failure, and severe COVID-19 pneumonia. This case illustrates the challenges to both the patient's access and management of the unknown drug-to-drug interactions of different treatment regimens in a lupus nephritis patient with disseminated TB and heart failure who developed and eventually recovered from severe COVID-19 infection. Management should be individualized to achieve disease control while minimizing adverse events.

Disclosure Statement. The authors declare no competing interest.

Funding. No funding was received by the authors for this work.

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