CASE REPORT

A case of lupus nephritis flare-up in severe COVID-19 infection

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SUMMARY
The novel Coronavirus disease 2019 (COVID-19) had rapidly spread and became a worldwide pandemic since its detection in Wuhan, China. The disease has caused significant morbidity and mortality, particularly among patients with comorbidities. The current treatment involves supportive management alongside antiviral therapy and immunosuppressant therapy in severely affected patients. We describe a case of a patient with underlying lupus nephritis (LN) who presented with severe COVID-19 infection and comorbid LN flare with acute kidney injury (AKI). The patient was treated with antiviral therapy, Favipiravir, considering his risk of developing severe COVID-19 infection. As the patients would usually have AKI alongside LN flare, we administered initial steroid therapy at a lower dose (Methyprednisolone 50mg daily) and oral hydroxychloroquine despite the initial concerns on immunosuppressant usage in COVID-19 infections. Although our patient recovered relatively well from COVID-19 infection, he continued to have positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swab for COVID-19 up to 29 days of illness. His kidney function stabilised despite having persistent nephrotic range proteinuria. Hence, the attending team decided to pulse the patient with a high dose steroid (IV Methyprednisolone 250mg OD for three days) after two weeks of illness despite the persistent positive swab. The patient's condition continued to improve, and this case illustrates an approach in treating COVID-19 with concomitant active immune-mediated glomerulonephritis. We find that it is safe to institute high dose immunosuppressant in recovered COVID-19 patients two weeks after the illness.

INTRODUCTION
The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 2 million people since its discovery in December 2019. The disease is associated with significant mortality and morbidity, especially among critically ill patients. Acute kidney injury (AKI) is common in COVID-19 patients, and around 20% of COVID-19 critical care admission require renal replacement therapy.1 There is a lack of evidence on the optimal treatment in immune-mediated kidney disease in COVID-19 due to its novelty and limited data available. We describe a case of symptomatic COVID-19 infection with concomitant relapse of lupus nephritis (LN) presenting with AKI. In this case, we highlight the difficulty in initiating immunosuppression treatment for LN in symptomatic COVID-19 infection.

CASE REPORT
A 30-year-old Indian immigrant with a background history of LN presented with a three-day history of fever, cough with exertional dyspnoea, vomiting and diarrhea. He developed multiple pustular skin lesions on his upper and lower limbs five days before admission. He denied any history of hair loss or Raynaud’s phenomenon and no history of nephrotoxic drug exposure. In the last three months, he had defaulted his immunosuppressive medications (prednisolone and mycophenolate mofetil).

He looked lethargic and dehydrated with hypotension (76/49mmHg) and had tachycardia (120 beats/minute) on admission. His blood pressure responded to normal saline resuscitation and improved to 105/71mmHg. He was febrile (39.2° Celsius) with good oxygen saturation on room air. His right elbow was swollen and warm with pus discharge. There was also presence of multiple minor ulcerated wounds on bilateral feet and buttocks (Figure 1 A, B). He also had pitting oedema of bilateral legs. There were no oral ulcer, malar rash, or lymphadenopathy. The rest of the examination was unremarkable.

The patient underwent the reverse transcriptase-polymerase chain reaction (RT-PCR) test through the nasopharyngeal swab because of positive COVID-19 contact history. He was tested positive with an initial Cycle Threshold (Ct) value of 26. His blood investigations revealed AKI with hyperkalaemia (Table I). However, there was no metabolic acidosis on blood gas analysis. Initial full blood count showed hypocromic microcytic anaemia with haemoglobin of 10.2 g/dL, a raised white cell count of 37.8 x 10⁹ (predominantly neutrophilia), absolute lymphocyte count of 1.2. Serum procalcitonin and C-reactive protein were 10.5ng/L and 33.8mg/dl, respectively. No evidence of haemolysis on peripheral blood film and serum lactate dehydrogenase and bilirubin levels were normal.
Further investigations showed hypocomplementemia with a high titre of anti-dsDNA suggestive of a lupus flare. The initial urine protein creatinine index (PCI) result was 0.14 g/mmol creatinine, but it rose to nephrotic range later. His chest radiograph at admission was normal (Figure 2) but the computed tomography scan of the chest revealed ground glass opacities at the periphery of the lower zone of the right lung (Figure 3). Additionally, there was no intra-articular collection or deep-seated abscess found on ultrasound at the region of the elbow. Skin biopsy results confirmed the presence of abscess without evidence of vasculitis. The skin biopsy culture and the blood culture were both negative.

The patient was treated for COVID-19 infection with concurrent sepsis, LN flare and AKI. Due to the concerns of COVID-19 deterioration, he was started on the new antiviral agent, favipiravir, with a loading dose of 1600mg twice daily followed by 600mg twice daily for four days. Intravenous cefazolin was also commenced. Despite the initial concern on initiating steroid in active COVID-19 infection, the managing team decided to control his lupus flare with a lower dose of steroid (intravenous methylprednisolone 50mg once daily) throughout hospitalisation in addition to oral hydroxychloroquine 200mg once daily. Venous thromboembolism prophylaxis was also given because of a
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The patient had a high D-dimer of 6.91 ug/ml and marked hypoalbuminemia (serum albumin 13 g/l). The patient was nursed in the critical care ward, and his general condition improved during the hospitalisation. He remained afebrile and did not need an increase in oxygen requirement. His kidney function improved, and septic parameters normalised on day 10 of hospitalisation (Table I). Perindopril 4mg once daily was started after renal function normalised. He was discharged after 18 days of hospitalisation with oral prednisolone 30mg daily and was scheduled for an outpatient nephrology clinic follow up.

However, the patient was readmitted two days later due to worsening pedal oedema. He had no further respiratory symptoms, and repeated chest radiograph did not show any worsening pneumonia. Despite a stable kidney function, his biochemical parameters revealed a persistent nephrotic syndrome. Although his repeat nasopharyngeal swab for RT-PCR test was still positive for COVID-19, the disease was considered inactive due to the absence of symptoms and signs of deterioration. Therefore, the decision was made to induce his LN into remission with IV Methylprednisolone 250mg daily for three days, followed by oral prednisolone of 0.5mg/kg along with mycophenolate mofetil. He was discharged after his fluid overload stabilised.

Unfortunately, he required the third admission due to lower limb cellulitis, requiring one week of intravenous antibiotics in which he had a good recovery. His RT-PCR remained positive on the 29 days since the first illness, but there was no respiratory symptoms progression. The Ct value for his recurrent admission was of similar value, 27 and 25 for his

Fig. 3: Contrast-enhanced computed tomography of the chest showed ground glass opacities at the right lower zone involving the lung periphery (white arrow).
second and third admission, respectively. His kidney function remained stable, but urine PCI was persistently in the nephrotic range with a slow improvement of serum albumin. Due to immigration rules, the patient was discharged to his home country after the completion of antibiotics.

DISCUSSION
There is limited evidence on the treatment of COVID-19 with concomitant immune-mediated kidney disease relapse. Numerous routine therapeutics and diagnostic procedures are being reconsidered as unsuitable during the active COVID-19 infection based on expert opinions and guidelines. We approached this case by prioritising the treatment of COVID-19 and, at the same time, instituting immunosuppression at a reduced dose. We also modified our diagnostic strategy to limit the spread of the disease.

The usage of antiviral treatment in COVID-19 was drawn from experience in managing the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) pandemic. We treated our patient with the antiviral favipiravir for the COVID-19 infection even before it was widely used as a standard treatment for COVID-19. Treatment that includes favipiravir has been shown to shorten the median length of viral clearance compared to lopinavir/ritonavir and was also associated with faster viral clearance. The drug’s side-effect profile also seems acceptable. Favipiravir has since been incorporated into Malaysia’s COVID-19 management guideline, but caution was given to its usage in patients with AKI due to its renal excretion. Although favipiravir and its active metabolite concentration were high in patients with mild to moderate renal impairment, the range is expected to be safe. Neither renal dose adjustment nor renal adverse effect was mentioned in the literature, and patient with lower glomerular filtration rate (GFR <20mL/min) was excluded from clinical trials. Our case showed no worsening of kidney function or side effects while on favipiravir despite the AKI.

Before RECOVERY trial, the use of steroids in COVID-19 patients was highly debated as the suppression of cellular immunity was thought to have contributed to a poor outcome for COVID-19 infections. The usage of steroids in the recent novel coronavirus infections, i.e., MERS and SARS, has caused delayed virus clearance, and many results pointed towards harm. However, early small studies in severely ill COVID-19 patients showed positive outcome with the use of steroids. It was confirmed later in a large randomised controlled trial, RECOVERY, which has significantly changed the practice in treating COVID-19. The use of dexamethasone at a dose of 6mg daily has proven to reduce mortality in COVID-19 patients who require respiratory supplementation.

Our patient was at risk of developing end-stage kidney disease due to his active LN without any immunosuppression; hence we decided to treat him with IV Methylprednisolone at 50mg daily for the renal indication. Steroid administration has become the standard of treatment for COVID-19 patients with hypoxia, where low dose dexamethasone or methylprednisolone are routinely given. However, in immune-mediated kidney disease with concomitant COVID-19 infection, many guidelines emphasised individualised immunosuppressive treatment for both steroid and other modalities and suggested a lower dose of steroids during active infection. Instead of administering high dose steroid pulses, we gave intravenous methylprednisolone at a lower dose equivalent to prednisolone 1mg/kg/d. The mycophenolate mofetil was discontinued due to active COVID-19 and sepsis.

Among patients with simultaneous COVID-19 infection and active immune-mediated glomerulonephritis, the optimal timing of immunsuppression intensification is unknown, especially among patient with concurrent sepsis. The dose of steroid in inducing remission in LN is much higher than the dose administered for COVID-19 infection, and the consequence of such dose on virus clearance is unknown, especially if administered early when the viral burden is high. In our case, we initiated pulse intravenous methylprednisolone (250mg/d for three days) during his second admission, 20 days after his COVID-19 illness. His RT-PCR remained positive with a Ct value of 27 but active COVID-19 infection cannot be proven without a viral culture. Ct values that are generated by qualitative PCR assays are affected by multiple factors and does not reliably correspond to viral load. The Centre for Disease Control and Prevention (CDC) suggested discontinuation of isolation after ten days for mild COVID-19 infection and up to 20 days for severe infection, suggesting a complete recovery and possible arbitrary non-infectious state. The difficulties in determining the clearance of infection will ultimately rely on the overall patient’s clinical assessment as performing viral culture is labour-intensive and not easily available. Ct value may be of help, but its limitation needs to be recognized.

One study has shown that the median duration of virus shedding was eight days from symptoms onset. The probability of detecting the virus in culture dropped below 5% after 15.2 days of post-onset of symptoms suggesting low viral burden, especially in patients with symptoms.
resolution. Hence, we believe that initiating high dose immunosuppression after two weeks of illness will be safe in recovered COVID-19 patients. We believe that the initiation of mycophenolate mofetil for consolidative treatment after the steroid pulse is also appropriate due to its oral route delivery, hence reducing contact with health service compared to cyclophosphamide that requires parenteral treatment and a more intense immunosuppressive agent.

CONCLUSION
In managing LN relapse with AKI in COVID-19 patients, it is important to concentrate on any reversible cause of the kidney injury and prioritise managing the COVID-19 before treating the LN. Initiation of steroid has now been proven to be helpful in oxygen dependent active COVID-19 infection and the benefit may also extend to patients with concomitant immune-mediated kidney disease. Additionally, treatment with high dose immunosuppressive treatment after 14 days of COVID-19 illness is acceptable in lupus nephritis flare-up.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

REFERENCES