Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Case Report

Combined intravenous immunoglobulin and baricitinib treatment for severe COVID-19 with rhabdomyolysis: A case report

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Since December 2019, the outbreak of coronavirus disease 2019 (COVID-19) has spread rapidly around the world. The severity of COVID-19 ranges from asymptomatic carriers to severe acute respiratory distress syndrome (ARDS). Accumulating evidence has shown that COVID-19 may be associated with multiple organ complications including cardiac injury, viral myositis and neurological deficits. Numerous laboratory biomarkers including lymphocytes, platelets, lactate dehydrogenase and creatine kinase (CK) have been associated with the prognostic outcomes of patients with COVID-19. However, dynamic correlations between levels of biomarkers and clinical course have not been studied.

Herein, we report a 74-year-old female patient with severe COVID-19 which progressed to ARDS requiring intubation and mechanical ventilation. The laboratory findings showed lymphopenia, hypogammaglobulinemia, and elevated inflammatory biomarkers and CK. She received intensive therapy with hydroxychloroquine, lopinavir/ritonavir, and azithromycin with limited effects. Immunomodulatory treatments with high dose intravenous immunoglobulin and baricitinib were prescribed with satisfactory biochemical, radiographic and clinical recovery. We found an interesting correlation between serum CK elevation and inflammatory biomarkers, which reflected clinical improvement. This case demonstrates that inflammatory biomarkers,

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cytokines, and CK level correlated with disease severity and treatment response, and combined use of intravenous immunoglobulin and baricitinib is a potential treatment in patients with severe COVID-19.

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has caused an ongoing pandemic since the first case was reported in December 2019.[1,2] Patients with COVID-19 have variable clinical manifestations including asymptomatic infection, mild upper airway symptoms, critical illness with acute respiratory distress syndrome (ARDS), and death.[3] Common clinical symptoms include fever, fatigue and dry cough, although gastrointestinal symptoms with anorexia, diarrhea, nausea and vomiting have also been reported.[4] Laboratory findings include leukocytosis, lymphopenia, and elevation of D-dimer, creatinine and creatine kinase (CK) in patients with severe COVID-19.[2,4]

Herein, we report a case of severe COVID-19 complicated with ARDS who received high-dose intravenous immunoglobulin (IVIg) and the Janus kinase (JAK) inhibitor baricitinib with significant laboratory and clinical responses. During treatment, there were two episodes of CK elevation. The first episode was positively associated with levels of inflammatory biomarkers and CK, and improved with supportive care, IVIg and baricitinib, indicating possible virus-related rhabdomyolysis. The second episode resolved after broad-spectrum antibiotic treatment and down-titration of the dose of baricitinib, and it may have been associated with secondary infection and baricitinib usage. The dynamic change in serum CK level may be able to predict disease severity and favorable treatment response to COVID-19 infection.

Case report

In mid-March 2020, a 74-year-old female patient was admitted to a hospital in southern Taiwan due to a close contact history with her daughter, a confirmed case of COVID-19. They had traveled for 10 days to eastern Europe in early-March 2020 with a tour group. The patient had type 2 diabetes mellitus and hypertension. She denied fever, productive cough, myalgia, dyspnea, or diarrhea during her travel. Her daughter, with whom she stayed during the whole trip, had productive cough and fever for a few days before arriving in Taiwan and was admitted to the hospital for definite COVID-19.

The patient developed a fever on admission, and her oxygen saturation was 97% under ambient air. Chest radiography revealed increased infiltration in the left lower lung. A laboratory examination revealed leukocytosis with mild lymphopenia (white blood cells 10.35 K/uL, Seg. 79.3%, Lym. 12.9%, lymphocyte count 1335/uL). The level of high-sensitive C-reactive protein (hsCRP) was within normal range (0.49 mg/dL, reference range $<$ 1 mg/dL). SARS-CoV-2 was identified using a reverse transcriptase polymerase chain reaction (RT-PCR) assay from an oropharyngeal swab on the day of admission, and the diagnosis of COVID-19 was confirmed.

On day 1 of hospitalization, she received ceftriaxone and oseltamivir, but the fever persisted. Hydroxychloroquine and lopinavir/ritonavir were prescribed on day 3, and cefepime and azithromycin were prescribed to replace ceftriaxone on day 6 for recurrent fever. However, severe lymphopenia progressed (lymphocyte count 476/uL). On day 7 of hospitalization, dyspnea with desaturation developed. A chest radiograph revealed worsened interstitial infiltrates and opacities over both lungs. Elective intubation was performed. She was then admitted to the intensive care unit for ARDS with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) of around 118 mmHg.

She received mechanical ventilation with inhaled nitric oxide and escalation of empirical antibiotics for broader coverage and poor oxygenation. Nevertheless, the P/F ratio rapidly worsened to 63 mmHg. The fever persisted with mildly elevated procalcitonin (0.545 ng/mL, reference range: $<$0.5 ng/mL) and markedly increased hsCRP (19.96 mg/dL). Notably, the serum CK level progressively increased from 61 U/L at admission to 1643 U/L, and the elevated serum creatinine level increased from 0.8 at baseline to 1.3 mg/dL. No obvious elevation of CK subtype CK-MB or troponin-T level was observed (CK-MB 9.93 ng/mL and troponin-T 38.3 ng/mL). She had no history of other pathogen infections, seizure, or medication exposure including neuromuscular blockade. The patient received cisatracurium in continuous infusion with a daily 1-h break, with a mean daily dose of 96—192 mg/day. Mild hypotension with normal lactate level was noted, so she was given low dose norepinephrine and gentle hydration. In addition, hypogammaglobulinemia (IgG 509 mg/dL, reference range: 700～1600 mg/dL) was found with severe lymphocytopenia. Due to an increased level of IL-6 (363.14 pg/mL, reference range: not detectable), suspected cytokine storm syndrome caused by both COVID-19 and secondary bacterial infection, IVIg was initiated on day 11 of hospitalization, with a 4-day course (total dose 2 g/kg). Defervescence was achieved on day 13 of hospitalization with decreased levels of CK (83 U/L) and hsCRP (2.92 mg/dL) and normal procalcitonin (0.443 ng/mL). The IL-6 level decreased (25.44 pg/mL) with mildly elevated CK (292 U/L). Due to persistent positive RT-PCR assay results of pharyngeal swab specimens, prolonged viral shedding with hyperinflammation was suspected. The JAK inhibitor baricitinib 4 mg per day was prescribed.

However, the serum level of CK level increased to another peak value of 1663 U/L. We adjusted baricitinib from 4 mg to 2 mg per day and escalated broad-spectrum antibiotics with coverage of both bacteria and fungi due to suspected baricitinib-related or secondary infection-related CK elevation. The level of CK then gradually returned to normal range.

Serial chest radiographs revealed resolution of infiltrates over both lungs with improved oxygenation demand (decreased fraction of inspired oxygen from 80% to 35%) and P/F ratio, as shown in Fig. 1. Improvements in inflammatory biomarkers (hsCRP 1.03 mg/dL, procalcitonin 0.453 ng/mL, and IL-6 8.25 pg/mL) were observed the following week. She was extubated after 23 days of intubation and 29 days after admission, without uncontrolled secondary infection. The total duration of cisatracurium use is 18 days, with gradual down-titration of the dosage. RT-PCR results of sputum from nasal and throat swabs were negative from day 43 of hospitalization. A trend was found between CK and inflammatory biomarkers including hsCRP, procalcitonin and IL-6, as illustrated in Fig. 2. Detailed data of CK, hsCRP, procalcitonin and IL-6 are listed in the Supplement.

Discussion

There are two important findings in this case with COVID-19 complicated with severe ARDS. First, serum CK level and inflammatory biomarkers may correlate with disease severity and treatment response. Second, COVID-19 was successfully treated with high-dose IVIg and baricitinib, which resulted in a favorable recovery without serious sequelae or uncontrolled secondary infection.

Virus-associated rhabdomyolysis, which has been described and is most commonly seen in influenza A and B viruses infection,[5—7] may have been implicated in the first peak of CK level in our patient because of rapidly deteriorating clinical symptoms and probable cytokine storm syndrome. A previous study reported that the initial peak level of CK was a predictor of mortality in COVID-19.[8] The possible pathophysiology of viral-related rhabdomyolysis may be direct muscle invasion by the virus, inflammation reaction resulting in collateral muscle damage, and viral toxins causing direct muscle injury.[9] A decline in serum CK level has been significantly correlated with the treatment response to COVID-19 infection.[10] It is possible that cisatracurium would worsen rhabdomyolysis, but we considered cisatracurium use is not the major contributing factor of CK elevation since the dosage of cisatracurium used was within even below the suggested mean maintenance dosage (3 mcg/kg/min, 259.2 mg per day concerning the patient's body weight).

The clinical manifestations of symptomatic COVID-19 infection are considerably different between patients with severe disease and those with non-severe disease. Lymphopenia, prolonged prothrombin time and elevated lactate dehydrogenase are the most common laboratory abnormalities.[3,4] The severity of lymphopenia and elevation of CK level have been significantly correlated with the clinical status and mortality rate in patients with COVID-19 infection, and thus may be able to predict treatment response.[3,4,11]

There is currently limited effective treatment for COVID-19. The short-term use of dexamethasone has been shown to lower the 28-day mortality rate in COVID-19 patients with oxygenation support demand.[12] However, the therapeutic benefits of other medications targeting COVID-19 including lopinavir/ritonavir, azithromycin and hydroxychloroquine are still uncertain.[13] Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, is a potential candidate for it anti-inflammatory effect and reported effective on 44-year-old woman with severe COVID-19 disease requiring mechanical ventilation in Taiwan with several international clinical trials ongoing.[14] IVIg has both anti-inflammation and immunomodulation effects and also assists in humoral immunity and hypogammaglobulinemia. Accumulating evidence supports that IVIg is beneficial for patients with SARS-CoV-2-induced hyper-inflammation.[15—18] A randomized controlled study of IVIg treatment in patients with severe SARS-CoV-2 pneumonia has been initiated (NCT 04261426).

Baricitinib, a janus kinase (JAK) inhibitor, is regarded to be a possible candidate for the treatment of severe COVID-19 patients via the inhibition of the AP2-associated protein

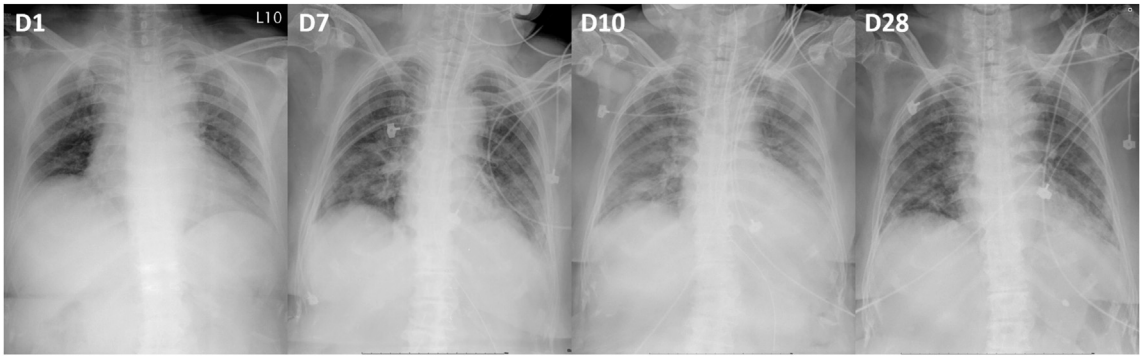

Figure 1 Serial changes in chest radiographs during hospitalization. Starting with left lower lung infiltrates from admission (D1), the patient had progressively increased bilateral middle-lower infiltrates, eventually requiring intubation with mechanical ventilation (D7). Diffuse bilateral infiltrates were noted before intravenous immunoglobulin (IVIg) treatment (D10). These improved, however residual infiltrates persisted after clinical improvement and before extubation (D28). D1: Admission, D7: after elective intubation, D10: before intravenous immunoglobulin (IVIg) treatment, D28: before extubation.

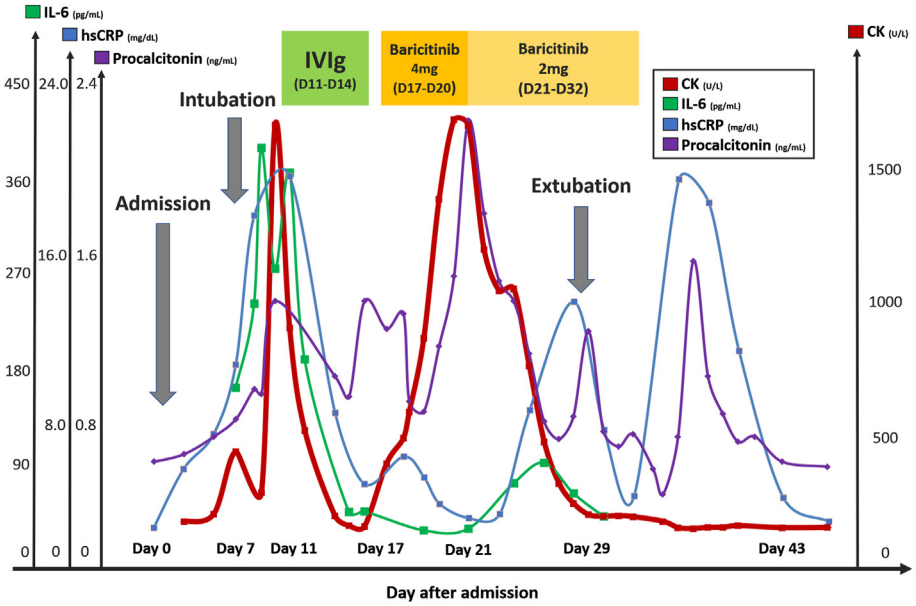

Figure 2 Trends and relationships among creatine kinase (CK), interleukin-6 (IL-6), high-sensitive C-reactive protein (hsCRP), and procalcitonin with major clinical events: Day 0: admission; Day 7: intubation; Day 11: initiation of IVIg; Day 17: initiation of baricitinib; Day 21: dose adjustment of baricitinib; Day 29: extubation; Day 43: RT-PCR results were negative, indicating viral clearance. Reverse-transcriptase-polymerase-chain-reaction (RT-PCR), intravenous immunoglobulin (IVIg).

kinase 1 (AAK-1) pathway and associated viral endocytosis.[19] In addition, its anti-inflammatory effect via the blockade of the JAK-STAT pathway may help to halt the cytokine storm in these patients.[20] However, because it inhibits interferon-associated anti-viral mechanisms and thereby increase the risk of herpes zoster and simplex infection,[21] the use of baricitinib in critical COVID-19 patients needs further clarification.[22,23] Regarding the safety of baricitinib, an increased risk of serious infections, reduction of neutrophils, and elevation of serum cholesterol have most commonly been reported. An abnormal CK level has rarely been reported, and most patients have been asymptomatic. Moreover, the phenomenon is usually transient.[21,24]

Limitations

This is a single case report, and thus the relationships of several laboratory markers lacked statistical significance. Analysis of larger prospective trials or retrospective cohorts may provide more clear and unbiased results. This clinical observation poses an interesting issue of COVID-19 with extra-pulmonary invasion and hyperinflammation, encouraging further detailed studies and promoting patient care.

Conclusion

In severe COVID-19 patients, fluctuations of CK level and inflammatory biomarkers may correlate with disease activity and treatment response. In addition, treatment with IVIg and baricitinib appears to be an effective and promising option to reduce viral infectivity, viral replication and inflammatory response. In conclusion, our case demonstrates a link between CK, inflammatory biomarker elevation, and clinical response in severe COVID-19 infection, and the satisfactory recovery with a combination of immunomodulatory regimens (both IVIg and baricitinib).

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

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