

High-dose N-acetylcysteine in an immunocompromised patient with COVID-19: a case report

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Case presentation

On 19 June 2022, a 45-year-old man was admitted to intensive care unit with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. His body mass index was 22.3. He had a history of hypertension, diabetes mellitus, hyperlipidaemia, and immunoglobulin A nephropathy. He had been receiving prednisolone and mycophenolate mofetil following a renal transplant. His baseline creatinine level was 203 $\mu\text{mol/L}$. Three doses of CoronaVac vaccine had failed to induce an antibody response.

The patient was in septic shock and had respiratory failure and acute renal failure. He had myopericarditis with elevated level of serum troponin I, diffuse ST elevation on electrocardiogram, and impaired left ventricular ejection fraction of 40% on echocardiogram. Coronary angiogram on 21 June 2022 was normal and myocardial biopsy revealed increased interstitial macrophages. Urine contained *Enterococcus faecalis* but no white blood cells on microscopy. Screening for other bacterial, viral or fungal co-infections was negative. He was prescribed intravenous remdesivir 200 mg once followed by 100 mg every 12 hours for four more doses and intravenous hydrocortisone 100 mg every 8 hours, and the nephrologist discontinued his mycophenolate mofetil treatment. He received broad spectrum antibiotics as directed by infectious disease specialists. Enoxaparin 60 mg was administered subcutaneously every 48 hours for prophylaxis of deep vein thrombosis. Infectious disease specialists did not recommend tocilizumab, baricitinib, monoclonal antibodies, or convalescent plasma.

The patient received intravenous high-dose N-acetylcysteine at a dose appropriate for treatment of paracetamol overdose as treatment of influenza-induced cytokine storm. Animal studies have shown that an oral dose of N-acetylcysteine 1 g/kg/day improved the survival of mice with otherwise lethal influenza infection and was synergistic with oseltamivir with an endpoint survival of 100%.¹ Human oral availability of N-acetylcysteine is 6%

to 10%. We have reported previously successful treatment of a patient with 2009 H1N1 influenza virus pneumonia with N-acetylcysteine, administered as a 100 mg/kg continuous intravenous infusion daily for 3 days, with consequent suppression of fever and C-reactive protein concentration and corresponding clinical improvement.² The C-reactive protein of this patient reduced from 183 mg/L to 11.7 mg/L and fraction of inspired oxygen requirement from 1.0 to 0.35. The positive end expiratory pressure reduced from 18 cm H₂O to 10 cm H₂O. Nonetheless the patient experienced a relapse of cytokine storm and pulmonary deterioration following discontinuation of high-dose N-acetylcysteine therapy before viral clearance. The C-reactive protein rebounded to 132 mg/L and fraction of inspired oxygen requirement increased to 0.85 and positive end expiratory pressure requirement to 16 cm H₂O. Results for sepsis workup were negative. The patient responded to reintroduction of N-acetylcysteine therapy and showed no relapse of cytokine storm when it was discontinued after viral clearance.² The patient, with SARS-CoV-2 pneumonia, received an infusion of N-acetylcysteine 10 g in 500-mL 5% dextrose solution at 21 mL/hour for 2 days from 21 June 2022. C-reactive protein level reduced from 278 mg/L to 72 mg/L and procalcitonin level from >200 ng/mL to 33.33 ng/mL. Fraction of inspired oxygen requirement decreased from 0.6 to 0.35 and positive end expiratory pressure requirement from 10 cm H₂O to 6 cm H₂O over 2 days following high-dose N-acetylcysteine infusion. When the patient showed no signs of viral clearance on 26 June 2022 and antibodies against SARS-CoV-2 remained negative, we commenced maintenance treatment with N-acetylcysteine at 2.5 g in 250 mL 5% dextrose solution infused over 4 hours twice daily (100 mg/kg/day) from 26 June 2022 until viral clearance on 18 July 2022. The patient was weaned off inotropic agents and mechanical ventilation and became dialysis and oxygen supplement independent. He was discharged from the intensive care unit on 29 June 2022 and resumed immunosuppressive

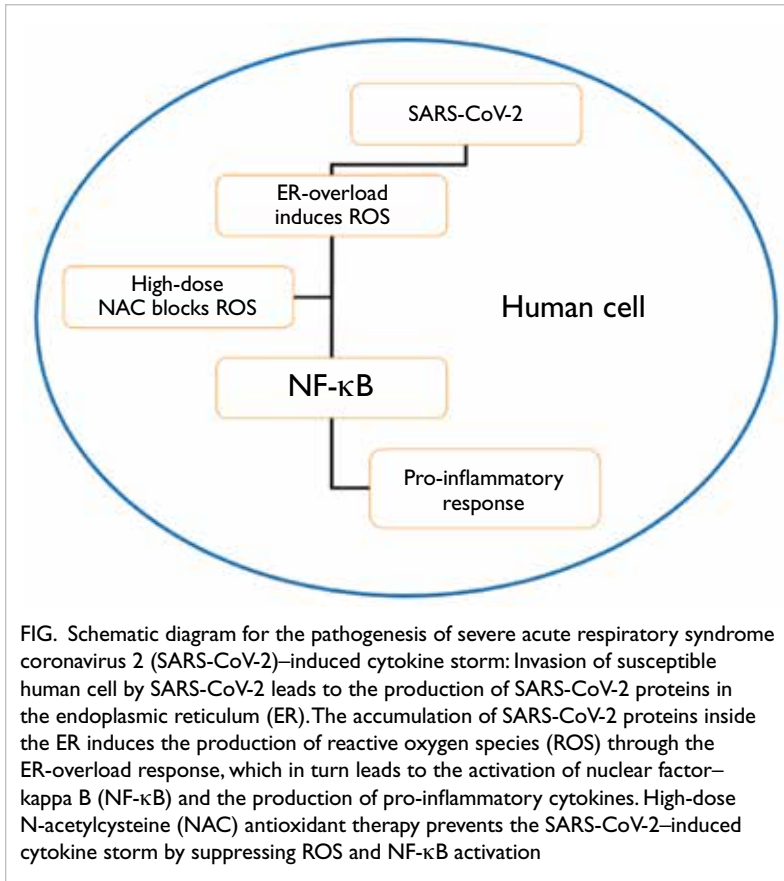


FIG. Schematic diagram for the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced cytokine storm: Invasion of susceptible human cell by SARS-CoV-2 leads to the production of SARS-CoV-2 proteins in the endoplasmic reticulum (ER). The accumulation of SARS-CoV-2 proteins inside the ER induces the production of reactive oxygen species (ROS) through the ER-overload response, which in turn leads to the activation of nuclear factor-kappa B (NF-κB) and the production of pro-inflammatory cytokines. High-dose N-acetylcysteine (NAC) antioxidant therapy prevents the SARS-CoV-2-induced cytokine storm by suppressing ROS and NF-κB activation

therapy on 30 June 2022. He was discharged home on 28 July 2022. The patient failed to develop any antibody response against SARS-CoV-2 throughout the infection (Fig).

Discussion

The SARS-CoV-2 mutates rapidly and relies on host cell factors and physiological processes for its entry, replication, and egress. These processes result in cytopathic damage, cytokine dysregulation, and death of host cells. These non-mutable key steps inside the host may be novel targets for future therapeutic strategies against these rapidly mutating viruses. The endoplasmic reticulum (ER) stores the majority of calcium ions and governs protein translation. The accumulation of proteins in the ER membrane, namely ER overload, leads to release of calcium ions from the ER and production of reactive oxygen species. This results in the activation of nuclear factor-kappa B (NF-κB) and the release of pro-inflammatory cytokines. The accumulation of coronavirus spike protein in the ER membrane results in an ER-overload response and cytokine storm.³ Open reading frame 3a (ORF3a) protein, ORF7a protein, membrane protein, and nucleocapsid protein of SARS-CoV-2 are also NF-κB activators. Of these four, ORF7a protein is the most potent NF-κB

inducer and pro-inflammatory cytokine producer.⁴ N-acetylcysteine is an antioxidant against reactive oxygen species and is a potent NF-κB inhibitor.⁵ Oral N-acetylcysteine administered at 600 mg thrice daily has been shown to reduce mortality in hospitalised SARS-CoV-2 patients.⁶ The clinical course of our patient suggests that high-dose N-acetylcysteine antioxidant therapy was able to control the cytokine storm of SARS-CoV-2 infection.

The SARS-CoV-2 virus mutates rapidly to produce new variants that can evade human antibody response and escape T-cell recognition and clearance. New variants cause challenges to the global effort in developing effective vaccines and medications against SARS-CoV-2. Current therapeutic strategies including vaccination, antiviral medications, and monoclonal antibodies are directed against the mutable targets of SARS-CoV-2. The SARS-CoV-2 vaccines and monoclonal antibodies that are highly effective against the SARS-CoV-2 wild-type (Wuhan-Hu-1) strain failed to confer adequate protection against the breakthrough infection nor prevent antibody evasion of omicron variants. Nonetheless high-dose N-acetylcysteine therapy acts directly against the reactive oxygen species and NF-κB activation in the ER-overload response of the host, independent of viral mutation. N-acetylcysteine has a complementary or even synergistic role to therapeutic agents that act on the mutable targets of SARS-CoV-2.

This case report illustrates that high-dose N-acetylcysteine can protect against SARS-CoV-2-induced cytokine storm in an immunocompromised host who could not elicit an antibody response. By controlling the cytokine storm, this patient coexisted with SARS-CoV-2 until viral clearance. As of 16 October 2022, only 23.3% of people in low-income countries had received at least one dose of coronavirus disease 2019 vaccine. If the protection afforded by high-dose N-acetylcysteine against severe complications of SARS-CoV-2 infection in patients without antibody response can be confirmed in prospective studies, non-fully vaccinated people and those with suboptimal antibody response to vaccination may benefit. This may include those with malignancies, on chemotherapy or immunosuppressive medications, with inborn errors of immunity, or with autoantibodies against type I interferons who are prone to critical SARS-CoV-2 pneumonia. N-acetylcysteine is safe and a category B drug for pregnancy. It is affordable for countries with limited resources and has the potential to end the coronavirus disease 2019 pandemic.

Author contributions

Concept or design: KY Lai.

Acquisition of data: All authors.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: KY Lai, SY Au.
 Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have declared no conflicts of interest.

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Ethics approval


The patient was treated in accordance with the Declaration of Helsinki and provided informed consent for all treatments and procedures, and consent for publication.

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- 3

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