Case report

# Cytokine storm and use of anakinra in a patient with COVID-19

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## SUMMARY

We present a case of a 50-year-old man with COVID-19 infection and acute respiratory distress syndrome as a result of a cytokine storm and use of anakinra, an interleukin 1-receptor antagonist that is normally used in the treatment of autoinflammatory disorders in adult patients. We saw a reduction in oxygen requirement and improvements in inflammatory markers and ferritin. Although we cannot determine its clinical efficacy from one case study, it may have a positive effect on the proinflammatory state that is associated with cytokine storm in COVID-19 infection.

## BACKGROUND

Mortality in COVID-19 is primarily caused by acute respiratory distress syndrome (ARDS) and a cytokine storm, resulting in a state of hyperinflammation and multiorgan failure.[1]

Evidence is emerging that screening patients with COVID-19 for hyperinflammation and then treating with immunosuppressive drugs may improve outcome.[1]

Anakinra is a recombinant form of human interleukin 1 (IL-1)-receptor antagonist that inhibits the activity of the proinflammatory cytokine IL-1 and is used in the treatment of autoinflammatory disorders (familial Mediterranean fever, systemic juvenile idiopathic arthritis and adult-onset Still's disease).[2] It has a good safety record including in patients with hyperinflammation and sepsis and its short half-life allows prompt discontinuation.[3]

We describe a case of life-threatening cytokine storm caused by COVID-19 infection that was treated with anakinra. Our patient improved on treatment but succumbed due to an intracerebral thrombotic event.

## CASE PRESENTATION

A 50-year-old male car mechanic had a background medical history of renal stones, cholecystitis and a body mass index of 30 kg/m$^2$.

He was admitted 7 days after symptom onset of sore throat, 5 days of fever and cough and 2 days of difficulty in breathing. On admission, he was tachycardic (heart rate 114 bpm), feverish at 39.4°C and oxygen saturation was 90% on room air. Arterial blood gas showed type 1 respiratory failure. Blood tests showed a white cell count (WCC) of $14.38\times10^9$/L, lymphocytes $1.72\times10^9$/L and C reactive protein (CRP) 358 mg/L. Chest X-ray (figure 1) identified bilateral suprahilar patchy opacities with reticulonodular shadowing mainly in the mid/lower and right lower zones. Nasopharyngeal swab was positive for SARS-CoV-2. He was treated as COVID-19 pneumonia with superadded infection (Procalcitonin (PCT) 0.99 ng/mL) and started on intravenous co-amoxiclav and supportive therapy with supplemental oxygen.

On day 4 of his admission, he deteriorated with increasing oxygen requirement (sats 85% on 60% supplemental oxygen). A computer tomography pulmonary angiogram (CTPA) (figure 2) identified no central pulmonary embolus, but extensive ground-glass opacification bilaterally and dense consolidation throughout both lower lobes. He was started on continuous positive airway pressure (CPAP) ventilation therapy and his antibiotics were changed. On day 6, he was admitted to intensive care unit (ICU) for ventilation due to further deterioration and poor compliance on CPAP. His inflammatory markers continued to rise despite antibiotics (WCC $22.71\times10^9$/L, CRP 478 mg/L, PCT 1.36 ng/mL), and he remained febrile.

He deteriorated further with fast atrial fibrillation, hypotension (requiring inotropic support) and persistent derangement in blood parameters (WCC $23\times10^9$/L, lymphocytes $1.17\times10^9$/L, CRP 448 mg/L, PCT 3.56 ng/mL, troponin 3965 ng/L, amino-terminal pro B-type natriuretic peptide 29 457 pg/ml, D-dimer 24 614 ng/mL, alanine aminotransferase 2207 iu/L, aspartate transaminase 5617 iu/L, lactate 2.7 mmol/L, fibrinogen 9.0 g/L). He developed acute kidney injury (creatinine 268 $\mu$mol/L) and required haemofiltration. Echocardiography showed dilated right ventricle (RV), preserved RV function, global left ventricular hypokinesia and severe left ventricular systolic dysfunction (ejection fraction 35%–40%), in keeping with myocarditis but acute coronary syndrome could not be excluded and as such, he was started on dual antiplatelet therapy and unfractionated heparin aiming for full anticoagulation.

On day 9, there was no clinical improvement and he was deemed to be in a cytokine storm (ferritin 85 789 $\mu$g/L, and CRP 338 mg/L). He was commenced on a 7-day course of intravenous anakinra (150 mg two times per day).

## OUTCOME AND FOLLOW-UP

Following commencement of anakinra, there was a noticeable reduction in oxygen requirements and, within 48 hours he had for the first time become afebrile and ferritin had significantly reduced to 5690 $\mu$g/L and CRP to 125 mg/L. After 1 week

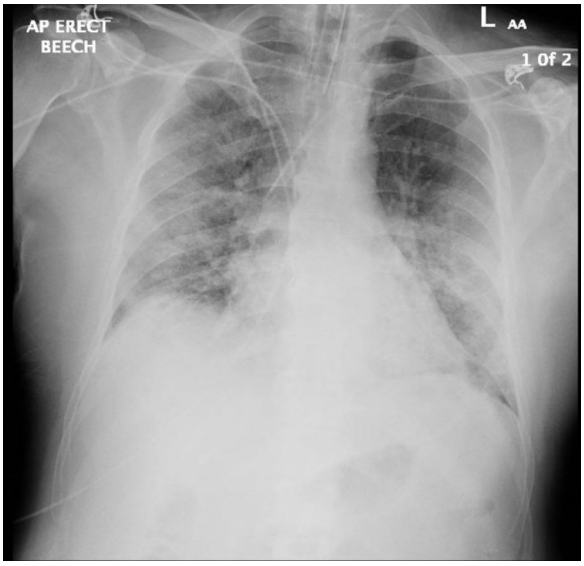


**Figure 1** Chest X-ray on day 6 of admission.

course of anakinra, his oxygen requirements were minimal with oxygen saturations of 93% on an $Fio_2$ of 0.25. His inotropic support was weaned and sedation stopped. His blood parameters had also improved (WCC $13.57\times10^9$/L, lymphocytes $1.91\times10^9$/L, CRP 81 mg/L).

On day 21 of his admission, having significantly improved including his chest X-ray, he was planned for extubation. Our patient suffered an acute intracerebral event with clinical evidence of a brainstem injury. A CT brain identified a sagittal sinus thrombus. He died the same day.

## DISCUSSION

COVID-19 can present from mild infection with fever and shortness of breath to severe interstitial pneumonia progressing to acute respiratory distress, multiorgan failure and death. COVID-19-associated pneumonia and ARDS have raised questions about the possible role of a cytokine storm in pathogenesis of SARS-CoV-2. Non-specific symptoms make it difficult to differentiate whether sepsis from bacteraemia is present, which can lead to delayed treatment. Our patient presented with persistent fever despite antibiotics, and deteriorating hypoxia, and extremely high inflammatory markers including ferritin and CRP.

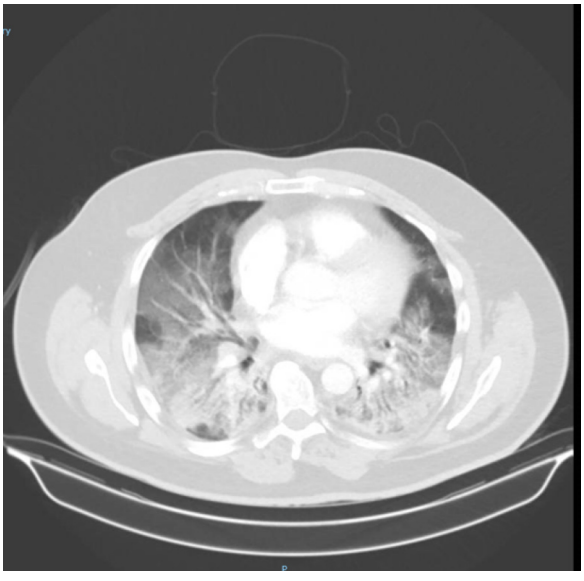

**Figure 2** Computer tomography pulmonary angiogram (CTPA) on day 3 of admission.

Cytokine storms were earliest described in haemophagocytic lymphohistiocytosis in relation to rheumatological conditions and following T cell immunotherapy (rituximab and alemtuzumab). They present similarly with fever, general malaise and fatigue but furthermore diarrhoea, vascular leakage, cardiomyopathy, lung injury and the synthesis of acute phase proteins. Activated immune cells, most importantly macrophages and epithelial cells, release high levels of IL-6, IL-10 and tumour necrosis factor-α (TNF-α).[4] Respiratory symptoms such as cough and tachypnoea can progress to ARDS.[5] Laboratory abnormalities that are common include cytopenias, elevated creatinine and liver enzymes, deranged coagulation, hyperferritinaemia and a high CRP.

How COVID-19 manifests pulmonary symptoms is not fully understood yet; however, it is thought to act similar to SARS-CoV-1 by acting on angiotensin-converting enzyme 2 receptor on alveolar epithelial cells activating IL-1B resulting in an inflammatory response in the lungs that leads to ARDS.[6]

More recently, cytokine storm has been implicated in viral infections such as avian influenza (H5N1) and SARS-CoV with the release of IL-10, IL-1B, IL-6, INF, TNF, chemokines and signs of acute lung injury progressing to ARDS with infiltration of monocytes and macrophages[7] and spillover of cytokines into the systemic circulation, producing systemic sepsis, as defined by persistent hypotension, hyperthermia or hypothermia, leucocytosis or leucopenia, and thrombocytopenia.[7]

In cytokine storms, IL-1B appears to be one of the main proinflammatory cytokines. Anakinra, an antagonist of IL-1 receptor (IL-1R), inhibits the release of IL-1B from macrophages and blockage of IL-1R has been associated with reversal of acute lung injury in avian influenza.[8 9]

During the COVID-19 pandemic, there are emerging case report and cohort studies demonstrating beneficial effects of anakinra.[10–12] San Raffaele Hospital, a tertiary healthcare centre in Milan, conducted a retrospective cohort study on the use of anakinra in patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU. Treatment with high-dose anakinra was safe and associated with clinical improvement. Seventy-two per cent of patients did not require mechanical ventilation and reduced CRP after 21 days.[10] Multiple clinical trials are underway for the use of anakinra in COVID-19 pneumonia.[13–15]

In our patient, there was reduction in the cytokine storm evidenced by a reduction in ferritin, fever and WCC after 2 days of anakinra. After 7 days, there was a significant reduction in oxygen requirement from 55% to 25% and an improvement in chest imaging with the consideration of extubation. However, he fatally suffered from sagittal sinus thrombosis that resulted in brainstem injury and death. There are reports of a higher incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia.[16] There are several theories for hypercoagulability; the release of cytokines, as seen in COVID-19, can increase the liver's production of clotting factors.[17] A cohort of patients in ICU were found to have raised fibrinogen and platelets with normal prothrombin time (PT) and Activated Partial Thromboplastin Time (APPT) suggesting systemic inflammation and hypercoaguabilty as opposed to other conditions such as disseminated intravascular coagulopathy.[18 19] Our patient had a resolution of fibrinogen, peaking at 9.0–4.8 g/L after 7 days of anakinra.

Our case suggests that the administration of anakinra in SARS-CoV-2-induced cytokine storm contributed to a significant clinical improvement. Anakinra is a cost-effective treatment in comparison with other potential biological treatments currently under clinical trials.[20 21] It also has a potentially safe side-effect profile. We suggest that earlier identification of patients developing cytokine storm and COVID-19 infection with monitoring of biomarkers (rising ferritin, CRP) and treatment with IL-1R antagonist anakinra may help prevent the sequelae of COVID-19 complications.

## Learning points

- Cytokine storm is a potentially life-threatening condition in COVID-19 pneumonia.
- Anticytokine therapy may provide benefit in these patients.
- Anakinra, an anti-interleukin 1 inhibitor led to an improvement in our patient with severe COVID-19 pneumonia associated with cytokine storm.

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**Contributors** PN gathered case report details from patient notes, researched topic and wrote up case report; HT continributed to clinical diagnosis, reviewed case report on multiple occasions, finalised final draft, researched topic; RM contributed to topic research and contributed to clinical diagnosis; JL redrafted case report and contributed to clinical diagnosis.

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