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Cytokine storm of a different flavour: The different cytokine signature of SARS-CoV-2, the cause of COVID-19, from the original SARS outbreak

Daniel O. Griffin\textsuperscript{a,b,*}, Alexandra Jensen\textsuperscript{c}, Mushroom Khan\textsuperscript{c}, Jessica Chin\textsuperscript{c}, Kelly Chin\textsuperscript{c}, Jennifer Saad\textsuperscript{c}, Ryan Parnell\textsuperscript{c}, Christopher Awwad\textsuperscript{c}, Darshan Patel\textsuperscript{c}

\textsuperscript{a} Department of Biochemistry and Molecular Biophysics, Columbia University Medical Center, New York, NY 10032, USA
\textsuperscript{b} Department of Medicine, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, New York, NY 10032, USA
\textsuperscript{c} Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

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Here we present a case series of three patients with COVID-19 (coronavirus disease 2019) who had a cytokine panel that revealed elevation of interleukin-6 (IL-6) but normal levels of interleukin-10 (IL-10), interferon-gamma (INF-\gamma) and interleukin-8 (IL-8), in contrast to the cytokine signature described in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). We also documented evidence of a compromised T-cell IFN-\gamma response in two of these patients.

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The clinical course of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can progress to involve significant complications that may be driven by a cytokine storm occurring during the second week of illness [1,2]. Decompensation and increasing oxygen requirement during the second week is associated with elevated interleukin-6 (IL-6) levels [3]. This cytokine storm appears to be different than that described for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in that there is elevated IL-6 rather than elevated levels of interferon-gamma (INF-\gamma) and interleukin-13 (IL-13) [4]. Here we present three cases of individuals who had full cytokine profiles revealing elevated IL-6 and low IFN-\gamma levels and evidence of compromised T-cell IFN-\gamma responses in contrast to the elevated levels of INF-\gamma and IL-13 levels described for SARS patients. The cytokine storm evident in COVID-19 that was observed in these three patients was characterised by an elevation of interleukin-6 (IL-6) but normal levels of interleukin-10 (IL-10), INF-\gamma and interleukin-8 (IL-8) and a compromised T-cell IFN-\gamma response to mitogen challenge.

Three patients admitted to Northwell Plainview Hospital in Plainview, New York (USA) tested positive for COVID-19 and had COVID-19 bilateral pneumonia with requirement for supplemental oxygen. The patients progressed to severe respiratory failure. During what was assumed to be the cytokine storm phase, based on laboratory parameters and a rising oxygen requirement, the patients received intravenous steroids (methylprednisolone 1–2 mg/kg per day x 5–8 days) and the IL-6 receptor antagonist tocilizumab 400 mg intravenously once. All three patients had elevated levels of IL-6 but low levels of other cytokines including IFN-\gamma and IL-13 (Table 1). Two of the patients also underwent testing with an interferon release assay to assess for latent tuberculosis and were observed to have a compromised T-cell IFN-\gamma response as assessed by mitogen challenge (Table 1).

Case 1: a 53-year-old male with no significant past medical history presented with 5 days of fever, malaise and difficulty breathing. On admission, he had a heart rate of 96 beats per minute (bpm), a respiratory rate of 14 breaths per minute (BPM), a temperature of 39.3 °C, a blood pressure of 122/51 mmHg and oxygen saturation on room air was 85%. He was admitted and treated with methylprednisolone 1 mg/kg intravenously daily but, with increasing oxygen requirement, an IL-6 level was drawn and the patient was treated with tocilizumab 400 mg intravenously once. He improved and oxygen therapy was able to be de-escalated.

Case 2: a 50-year-old male with a past medical history of hypertension, gastroesophageal disease and hyperlipidaemia was admitted with fatigue and hypoxemia. On admission, his heart rate...
was 114 bpm, respiratory rate 18 BPM, temperature 38 °C, blood pressure 122/78 mmHg and oxygen saturation on room air was 86%. He was admitted and treated with methylprednisolone 1 mg/kg intravenously but, with increasing oxygen requirement, an IL-6 level was drawn and the patient was treated with tocilizumab 400 mg intravenously once. He did not improve and was intubated and placed on mechanical ventilation. This individual had the lowest neutrophil-to-lymphocyte ratio (NLR) of the three individuals so it is not clear why he progressed to require mechanical ventilation. He had the highest body mass index (BMI) and the highest C-reactive protein (CRP) but only an intermediate IL-6 level, demonstrating even in this small series the variability of outcomes seen in COVID-19.

Case 3: a 45-year-old male with past medical history of asthma, gastroesophageal reflux, hyperlipidemia and lumbago was brought in by ambulance with cough, fever, difficulty breathing and hypoxemia. On admission, he has a heart rate of 115 bpm, respiratory rate 22 BPM, temperature 38.8 °C, blood pressure 124/86 mmHg and oxygen saturation on room air was 88%. He was admitted and treated with methylprednisolone 1 mg/kg intravenously daily but, with increasing oxygen requirement, an IL-6 level was drawn and the patient was treated with tocilizumab 400 mg intravenously once. He improved and oxygen therapy was able to be de-escalated. The patient was ultimately discharged on supplemental oxygen and steroid taper.

The cytokine storm associated with SARS-CoV-2 appears to be distinct from that seen in patients with SARS and MERS as evidenced by elevated levels of IL-6 in the context of low levels of IFN-γ and IL-8 [4,5]. Unlike other inflammatory conditions, such as acute respiratory distress syndrome (ARDS), MERS and SARS, we saw no elevation of interleukin-1 beta (IL-1β), suggesting that targeting the interleukin-1 (IL-1) pathway may not be of benefit in COVID-19 [6]. This cytokine signature is consistent with other reports describing the dysregulation of the immune response in patients with COVID-19 in Wuhan, China. It is not clear from these observations which cells are producing IL-6, as IL-6 may be produced by B-cells, T-cells, monocytes and even cells such as fibroblasts not normally appreciated to be part of the immune response [7]. There appears to be a delay in the onset of the cytokine storm relative to the onset of symptoms, but it does not appear that this is driven by ongoing antigenic stimulation due to viral replication based on prior studies of the viral kinetics [8]. Studies of mild cases show clearing of infectious virus soon after the first week, while hospitalised patients continue to have positive PCR tests well past the end resolution of symptoms [9,10]. It is not clear whether there is continued viral replication during the time of the described cytokine storm and whether interventions to address the hyperinflammatory state, such as steroids or IL-6 receptor inhibition, could lead to persistent viral replication [11].

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