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Cytokine storm of a different flavor: the different cytokine signature of SARS-CoV2 the cause of COVID-19 from the original SARS outbreak

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Running Title:

Cytokine elevations in COVID-19

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Highlights

- We present a case series of three patients with COVID-19 who had a cytokine panel which revealed elevation of interleukin-6 (IL-6), but normal levels of interleukin-10 (IL-10), interferon-gamma (INF-γ) and interleukin-8 (IL-8) in contrast to the cytokine signature

described in Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS).

- We also documented evidence of a compromised T-cell IFN-γ response in two of these patients.

- 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 of interleukin-1 (IL-1) pathway may not be of benefit in COVID-19.

Key-words: COVID-19, SARS-CoV2, cytokines, Interleukin-6, cytokine storm

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Research Letter

Abstract:

We present a case series of three patients with COVID-19 who had a cytokine panel which revealed elevation of interleukin-6 (IL-6), but normal levels of interleukin-10 (IL-10), interferon-gamma (INF-γ) and interleukin-8 (IL-8) in contrast to the cytokine signature described in Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). We also documented evidence of a compromised T-cell IFN-gamma response in two of these patients.

Letter

The clinical disease course of 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 Eastern Respiratory Syndrome (MERS) in that there is elevated IL-6 rather than elevated levels of interferon-gamma (INF-γ) and interleukin-13 (IL-13).(4) We present three cases of individuals who had full cytokine profiles revealing elevated IL-6 and low IFN- γ levels and evidence of compromised T-cell IFN-γ responses in contrast to the elevated levels of INF- γ and IL-13 levels described for SARS patients. The cytokine storm evident in COVID-19 that was observed in these three patients was characterized by an elevation of interleukin-6 (IL-6), but normal levels of interleukin-10 (IL-10), interferon-gamma (INF-γ) and interleukin-8 (IL-8) and a compromised T-cell IFN-γ response to mitogen challenge.

Three patients admitted to Northwell Plainview Hospital in Plainview, New York tested positive for COVID-19 and had COVID-19 bilateral pneumonia with requirements 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 400mg intravenously x1. All three patients had elevated levels of IL-6 but low levels of other cytokines including IFN-γ and IL-13 (table 1). Two of these patients also underwent testing with an interferon release assay to assess for latent tuberculosis and were observed to have a compromised T-cell IFN-γ 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 heart rate-96 beats per minute (bpm), respiratory rate-14 breaths per minute (BPM), temperature 39.3^0 C, blood pressure-122/51 mmHg and oxygen saturation on room air was 85%. He was admitted and treated with methylprednisolone 1mg/kg intravenously daily but with increasing oxygen requirements an IL-6 level was drawn and the patient was treated with tocilizumab 400mg intravenously x1. He improved and oxygen therapy was able to be de-escalated.

Case 2: A 50-year-old male with past medical history of hypertension, gastroesophageal disease, and hyperlipidemia was admitted with fatigue and hypoxemia. On admission heart rate-114 bpm, respiratory rate-18 BPM, temperature-38^0 C, blood pressure--122/78 mmHg and oxygen saturation on room air was 86%. He was admitted and treated with methylprednisolone 1mg/kg intravenously daily but with increasing oxygen requirements an IL-6 level was drawn and the patient was treated with tocilizumab 400mg intravenously x1. He did not improve and was intubated and placed on mechanical ventilation. This individual had the lowest neutrophil lymphocyte ratio (NLR) of these individual so it is not clear why this individual progressed to require mechanical ventilation. This individual did have the highest

body mass index (BMI), the highest C-reactive protein (CRP), but only an intermediate level of IL-6 and demonstrates 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 heart rate-115 bpm, respiratory rate-22 BPM, temperature-38.8^0 C, blood pressure-124/86 mmHg and oxygen saturation on room air was 88%. He was admitted and treated with methylprednisolone 1mg/kg intravenously daily but with increasing oxygen requirements an IL-6 level was drawn and the patient was treated with tocilizumab 400mg intravenously x1. He improved and oxygen therapy was able to be de-escalated. Pt was ultimately discharged on supplemental oxygen and steroid taper.

The cytokine storm associated with SARS-CoV2 appears to be distinct from that seen in the patients infected with SARS and MERS as evidenced by elevated levels of IL-6 in the context of low levels of IFN-γ and interleukin-8 (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 of 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 does appear to be a delay in the onset of the cytokine storm relative to 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 studies of hospitalized patients continue to have positive PCR tests well past the end resolution of symptoms.(9,

10) It is not clear if there is continued viral replication during the time of the described cytokine storm and if 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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Table 1: Patients with Cytokine Storm

Case (units) / (normal range)	1	2	3
Age	53	50	45
Body mass index (kg/m^2) / (18.5-24.9)	27*	37*	33*
eGFR (mL/min/1.73m^2) / (≥60)	104	78	100
D-dimer (ng/mL) / (≤229)	12377*	565*	10952*
Ferritin (ng/mL) / (15-150)	569*	655*	1309*
CRP (mg/dL) / (0.00-0.40)	1.54*	3.98*	1.69*
Neutrophil lymphocyte ratio (NLR)/ (≤3)	12.74/0.62=**20.5***	3.93/0.35=**11.2***	7.73/0.08=**96.6***
Cytokine (units) / (normal range)			
TNF-α (pg/mL) / (≤7.2)	<5	<5	<5
IL-2 (pg/mL) / (≤2.1)	<5	<5	<5
IL-12 (pg/mL) / (≤1.9)	<5	<5	<5
IFN-γ (pg/mL) / (≤4.2)	<5	5	<5
IL-4 (pg/mL) / (≤2.2)	<5	<5	<5
IL-5 (pg/mL) / (≤2.1)	<5	<5	<5
IL-10 (pg/mL) / (≤2.8)	18*	<5	6*
IL-13 (pg/mL) / (≤2.3)	<5	<5	<5
IL-17 (pg/mL) / (≤1.4)	<5	9*	<5
IL-1-β (pg/mL) / (≤6.7)	<5	<5	<5
IL-6 (pg/mL) / (≤2.0)	**42***	**79***	**114***
IL-8 (pg/mL) / (≤3.0)	<5	<5	<5
Quantiferon TB Plus	Indeterminant*	-	Indeterminant*
Quantiferon TB Plus Nil (IU/mL)	0.01	-	0.06
Quantiferon TB Plus TB1 minus Nil (IU/mL)	0.00	-	0.01
Quantiferon TB Plus TB2 minus Nil (IU/mL)	-0.01	-	0.00
Quantiferon TB Plus Mitogen minus Nil (IU/mL)	0.04	-	0.03

*abnormal value