SARS-CoV-2: A Storm is Raging

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Abstract

The pandemic coronavirus infectious disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is rapidly spreading across the globe. In this issue of the *JCI*, Chen and colleagues compared the clinical and immunologic characteristics between moderate versus severe COVID-19. The authors found that respiratory distress on admission is associated with unfavorable outcomes. Increased cytokine levels (IL-6, IL-10 and TNFα), lymphopenia (in $CD4^+$ and $CD8^+$ T cells), and decreased IFNγ expression in $CD4^+$ T cells are associated with severe COVID-19. Overall, this study characterized the cytokine storm in severe COVID-19 and provides insights into immune therapeutics and vaccine design.

A rapidly expanding pandemic

In early December 2019, several local health facilities first reported pneumonia cases of unknown origin in Wuhan, China. This new coronavirus infectious disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported on December 1, 2020 and identified as a previously unknown betacoronavirus (1, 2). Since then, studies have increasingly exhibited that SARS-CoV-2 can be transmitted effectively among humans through aerosol or fomite transmission (3-5). With transmission capabilities even before symptom onset (6, 7), the pandemic is rapidly evolving and expanding. As of March 25, 2020, a total of 414,179 confirmed cases of COVID-19 and 18,440 deaths have been reported across 196 countries and territories. Recent models indicated that as much as 86% of all infections early in the spread were undocumented, suggesting the real number of infections is likely much greater (8). As a public health emergency of international concern, COVID-19 was declared a pandemic by the World Health Organization. Public health authorities around the globe are now racing to contain the spread.

SARS-CoV-2: not a common cold

Coronaviruses are a family of enveloped RNA viruses broadly distributed in humans and animals that cause acute and chronic diseases. Of the six coronavirus species previously known to cause human diseases, four typically cause common cold symptoms and two – severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) – can cause fatal respiratory disease (9, 10). SARS-CoV-2 shares many similarities with SARS-CoV, which caused a global epidemic in 2002–2003, affecting more than 8,000 patients and causing 774 deaths in 26 countries (9). SARS-CoV-2 is closely related to two bat-derived SARS-like coronaviruses and SARS-CoV in phylogenetic distance

(11). SARS-CoV-2 shares the same cellular receptor angiotensin-converting enzyme 2 (ACE2) as SARS-CoV (12), suggesting a similar tropism and route of entry.

Although the majority of SARS-CoV-2-infected individuals may have no or mild diseases, SARS-CoV-2 infection is not simply a common cold. Despite similarities between SARS-CoV and SARS-CoV-2, SARS-CoV-2 is causing a global pandemic while SARS-CoV infection was limited to contained geographic regions. First, SARS-CoV-2 are infectious before symptom onset (6, 7), while SARS-CoV has no reported instance of transmission before the onset of symptoms (9). Up to 56% of SARS-CoV-2 infected individuals present without fever even on hospital admission (13), further increasing the difficulty of proactive entry health screening and containment. Second, the crude mortality rate of SARS-CoV-2 infection is estimated at 3–4%, which is remarkably higher than that of influenza infection (typically well below 0.1%) (14). Therefore, drastic quarantine measures have been implemented in multiple countries, including a record-breaking scale of travel restrictions within the community and between countries.

Eight days after symptom onset

Shortly after the outbreak, health care systems in affected areas are experiencing overwhelming demand for patient care. Even after suspending most non-critical medical care, the skyrocketing increase in COVID-19 cases paralyzes the health care system even in developed countries. As the magnitude of the outbreak exceeds health care capacities, point-of-care indicators which can distinguish severe versus moderate disease for immediate triage and clinical disposition become critically important to prioritize medical resources.

In this issue of the *JCI*, Chen et al. (15) compared clinical presentations of a total of 21 patients. These patients have an older age (average 56 years) with comorbidities (33%) and late presentations (~8 days after symptom onset). Chen et al. (15) categorized the disease

severity as severe versus moderate, defined by the presence of respiratory distress at presentation: peripheral capillary oxygen saturation (SpO2) ≤ 93% or respiratory rate ≥ 30 breaths per minute under ambient air, in line with the parameters outlined in the Chinese 6th edition guidelines. Chen et al. (15) found that the presence of respiratory distress on admission is associated with leukocytosis and increased inflammatory indicators (such as D-dimer and procalcitonin). These laboratory changes have been previously reported in COVID-19 patients requiring intensive care unit (ICU) admissions (1). Of note, the clinically confirmed cases presented in Chen et al. (15) had fever, respiratory symptoms, laboratory confirmed SARS-CoV-2 infection, radiologically confirmed pneumonia (by chest CT) and severity requiring hospital admission. Therefore, the clinical characteristics presented in this study represent the more severe end of COVID-19 confirmed cases with respiratory distress and pneumonia, which are not the same as mild or asymptomatic cases identified through contact tracing. Nevertheless, a simple emergency room triage using respiratory rate and pulse oximeter in high-risk COVID-19 patients ~8 days after symptom onset is correlated with an unfavorable outcome that likely requires mechanical ventilation and ICU admission.

Associations with disease severity

The two coronaviruses that have been known to cause fatal pneumonia, SARS-CoV and MERS-CoV, are associated with rapid virus replication, an elevation of pro-inflammatory cytokines, and inflammatory cell infiltration (16). In SARS-CoV infection, it was immune dysregulation, rather than the level of peak viremia, which induced insufficient type-I interferon (IFN) response (too-little-and-too-late), aberrant proinflammatory cytokine secretion by alveolar macrophages and subsequent CD4$^+$ and CD8$^+$ T cell dysfunction (17). Little is known about the determinants of disease severity and immune dysregulation in SARS-CoV-2 infection in humans. The study by Chen et al. (15) provides the window for us to examine the immune

dysregulations at 7–10 days of onset, when the cytokine storm rages and the respiratory distress peaks.

Cytokines and chemokines have long been understood to have an important role in immunity and immunopathology, but dysregulated and exuberant immune responses have been shown to potentially cause lung damage and diminished survival. In SARS-CoV-2 infected individuals, interleukin (IL)-6, IL-10 and TNFα surges during illness and declines during recovery. Patients requiring ICU admission have significantly higher levels of IL-6, IL-10 and TNFα and fewer CD4$^+$ and CD8$^+$ T cells (18). Further, the level of IL-6, IL-10 and tumor necrosis factor (TNF)-α inversely correlates with CD4$^+$ and CD8$^+$ T cell count (18), confirming previous animal studies that it is the cytokine storm which dampens adaptive immunity against SARS-CoV infection (17). In this issue of the *JCI*, Chen and colleagues (15) present one of the first studies comparing the immunologic characteristics between severe and moderate COVID-19. Despite an increase in white blood cell count, CD4$^+$ and CD8$^+$ T cell counts were significantly decreased in severe COVID-19 patients (p = 0.018, 0.035). Serum cytokine levels and analysis of lymphocyte composition on admission suggests that SARS-CoV-2 infection is associated with lymphopenia (particularly in CD4$^+$ T cells and CD8$^+$ T cells but not in B cells), overproduction of cytokines (IL-6, IL-2R (soluble IL-2 receptor), IL-10 and TNFα), and decreased IFNγ-expression in CD4$^+$ T cells in severe COVID-19 which correlated with disease severity of COVID-19 (Figure 1). Levels of IL-6, IL-2R, IL-10 and TNFα were mildly elevated or within the normal range in moderate cases, but markedly elevated in most severe cases. These cytokines are likely produced by highly inflammatory macrophages which have been implicated in cytokine storm (19). The total lymphocyte count, and specifically CD4$^+$ T cells and CD8$^+$ T cells were slightly lower in moderate cases and significantly decreased in severe COVID-19 (15). Most importantly, the authors found that IFNγ expression in CD4$^+$ T cells were lower (although not statistically significant, p = 0.063) in patients with severe versus moderate COVID-19. This

study demonstrates that cytokine storm is associated with COVID-19 disease severity, likely through increased pulmonary pathology, T cell depletion and CD4^{+} T cell dysfunction. These findings are in line with those of Diao and colleagues, which suggested that in addition to reduction in T cell counts, surviving T cells appear functionally exhausted (18).

Study Limitations

Studying the immunological features of COVID-19 presents new challenges and limitations. The statistical power of this study is severely hindered by the small sample size. Further, this study compares clinical presentations in moderate versus severe cases in high-risk populations and fails to present the clinical spectrum of the majority of SARS-CoV-2 infections, which is mild or asymptomatic, especially in young and healthy populations (15). Prospective studies which examine both innate and adaptive immune cell subsets and functions at different timepoints, such as early during the asymptomatic viremic stage, during respiratory distress and after recovery, may identify mechanisms driving immune dysregulation in patients who have different disease susceptibilities, such as children versus the elderly.

Taken together, SARS-CoV-2-induced cytokine storm is associated with disease severity and outcome. Understanding the immune dysregulation in patients with COVID-19 not only provides a greater understanding of SARS-CoV-2 pathogenesis but also identifies targets for immune therapeutics. While antiviral agents are currently being explored, the use of antiviral agents alone may not be sufficient to stop the cytokine storm, pulmonary destruction and respiratory distress in patients who presented late after infection. Targeted immunomodulation which reduces the cytokine storm may ameliorate pulmonary inflammation and hopefully improve mortality. Further studies on viral factors driving immune dysregulation may provide insights into shaping vaccine responses toward protective immunity.

Acknowledgements

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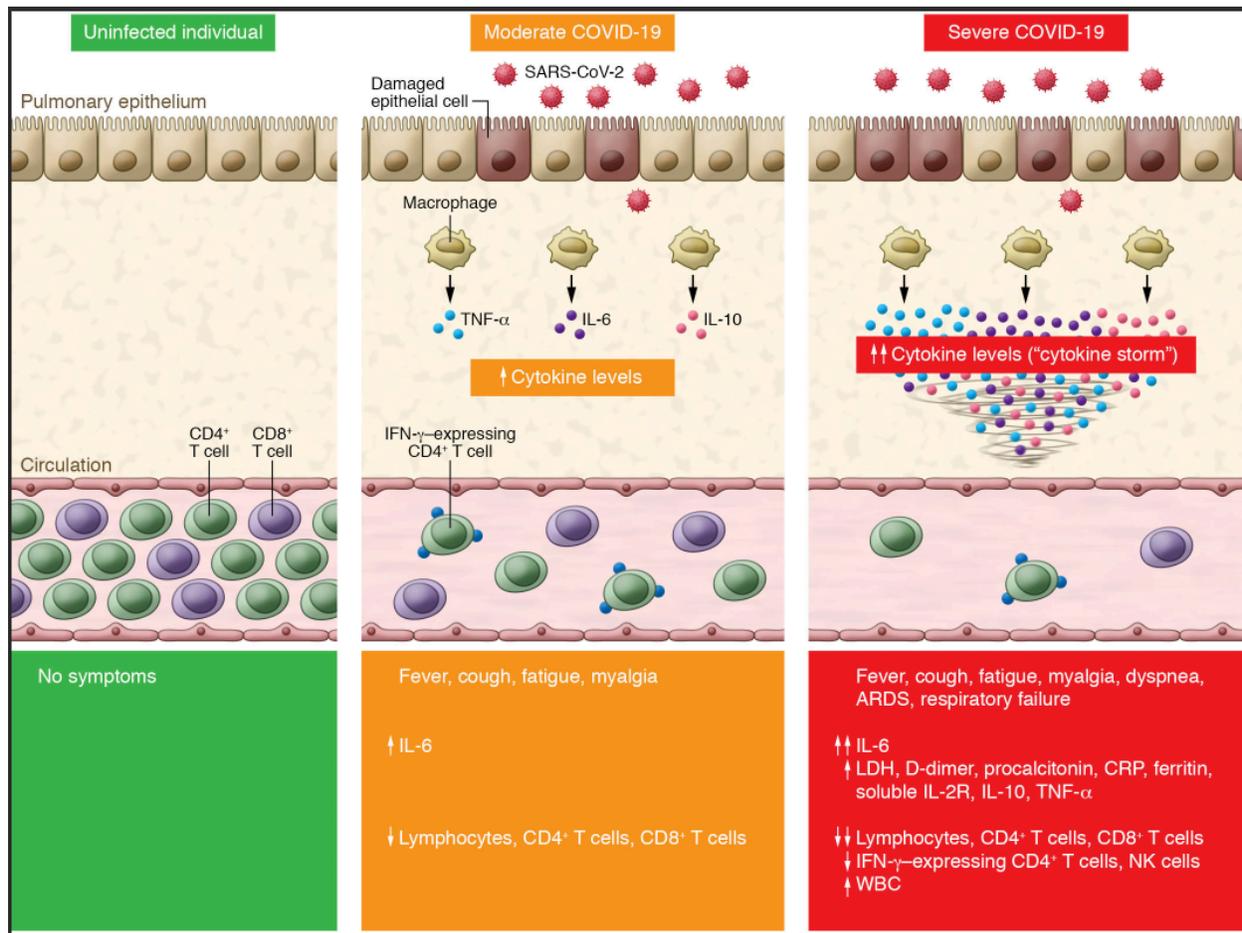
Figure 1. Cytokine storm and T cell lymphopenia is associated with COVID-19 disease severity. SARS-CoV-2 infection causes COVID-19. Compared to uninfected individuals (left panel), moderate COVID-19 cases exhibit an increase in IL-6 and a decrease in total T lymphocytes count, particularly CD4$^+$ T cells and CD8$^+$ T cells (middle panel). Severe COVID-19 cases have further increased production of IL-6, IL-2R, IL-10 and TNFα, while total T lymphocytes, particularly CD4$^+$ T cells and CD8$^+$ T cells, and IFNγ-expressing CD4$^+$ T cells markedly decrease (right panel). The level of cytokine storm and T cell lymphopenia is associated with pulmonary damage, respiratory distress and unfavorable outcome.