Immune Status of COVID-19 Patients with Reference to SARS and MERS

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Abstract

During this global pandemic of COVID-19 infection, it became well known that morbidity and mortality is especially high at the extreme of life especially in certain racial or ethnic groups like Americans and Africans. This is presumed due to low immunity associated with other comorbid conditions like diabetes, hypertension, cardiovascular disease, obesity and metabolic syndrome. But the information available on the immune status of COVID-19 patients is limited. Attempts must be made to enhance our understanding of the immune status of COVID-19 patients by revisiting our knowledge on the immune mechanisms of already known coronaviruses such as SARS-CoV and MERS-CoV. Early elevation of the serum levels of pro-inflammatory cytokines observed in SARS and MERS infection suggests a possible same type of cytokine storm-mediated lung damage in COVID-19 patients too. Dysregulation of interferon-1 response and downstream cascade in initial innate immune response at virus entry point has been related to lethal pneumonia in COVID-19 patients. Adaptive response of increased CD8+ levels in COVID-19 patients seems to be useful in mild cases where it causes deteriorating effects in progressed severe disease patients resulting in destruction of type 2 pneumocytes hence inability to regenerate the alveolar epithelium. A phenomenon called cytokine storm activates violent immunological reactions in the lung tissue resulting in ARDS followed by multiple organ system damages in COVID-19 patients. Several immune evading mechanisms are thought to be employed by severe respiratory syndrome virus-2 (SARS-CoV-2) that might have resulted in its extremely increased contagiousness probably related with its frequent RNA mutations. Failure to develop adequate virus limiting immune reactions by some cured patients warrant monitoring of all recovered patients. This rapid mini review is aimed to enhance our knowledge of the immune status of COVID-19 infected patients with reference to SARS-CoV and MERS-CoV.

Keywords: Immune status, COVID-19, SARS-CoV, MERS-CoV, coronavirus

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INTRODUCTION

Even though the current information on the host innate immune status of COVID-19 patients is limited, our knowledge on SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East respiratory syndrome) combined with preliminary findings of COVID-19 patients can provide us clues regarding the immune status of infected patients. Elevated total neutrophils and decreased total lymphocytes in COVID-19 patients presenting as mild and severe disease were found to be significantly different. Elevated neutrophils and decreased lymphocyte significantly related to disease severity and death. Early elevation in the serum levels of pro-inflammatory cytokines observed in SARS and MERS infection suggests a possible same type of cytokine storm-mediated lung damage in COVID-19 patients too.

Innate immune response

When the viral particle enters the respiratory epithelial cells, its antigen is rendered to the antigen presentation cells (APC), which is the first step in the execution of the body’s antiviral immune mechanism. Innate immune cells generally recognize the corona viral antigen by pathogen-associated molecular patterns (PAMPs). In the case of most RNA viruses including coronavirus, it is a well-known phenomenon that PAMPs which is the viral RNA or the intermediate structures during the viral replication processes such as dsRNA is recognized by various cytosolic RNA sensors and endosomal RNA receptors. This event of recognition is then followed by a number of down signaling pathways including nuclear translocation and transcription. In the nucleus, various transcription factors trigger the expression of Interferon 1 (IFN-1) along with other pro-inflammatory cytokines. This cascade of the event forms the first line of the defense system against the viral antigen at the point of entry. Dysregulation in this IFN-1 response and downstream cascade has been related to lethal pneumonia in COVID-19 patients.

Adaptive immune response

Th1 type immune reaction is the main component of adaptive immunity to most viral infections including coronaviruses. Like any usual acute viral infections, SARS and MERS also have the typical IgM and IgG antibodies in their antibody profile. IgM antibodies tailor out at the end of the 12th week of viral entry whereas IgG antibodies last longer. Preliminary test results in COVID-19 patients have shown peak IgM at day 9 followed by a shift to IgG by 2nd week. The latest reports show a reduced number of CD4+ and CD8+ lymphocytes in COVID-19 patients. Along with lower lymphocytes counts, sever cases have elevated leukocytes counts and neutrophil-lymphocyte-ratio (NLR) and also decreased number of monocytes, eosinophils, and basophils.

Previously, the initial rise in CD8+ cells has been associated with worse outcomes in the case of SARS and MERS. Details on whether such initial elevation of CD8+ relates the severity of disease in COVID-19 patients’ needs to be studied. Reduced CD8+ cells in severe cases of COVID-19 are thought to be involved in associated lung damage. Though protective, this CD8+ cells association with lung damage is attributed to the delayed or dysregulated immune response elicited by these cells. Therefore CD8+ T cell elevation, even though essential to keep the viral proliferation under control, has to be managed in order to prevent severe lung damage.

Cytokine storm

Adult respiratory distress syndrome (ARDS) is known to be one of the main causes of death in COVID-19 patients. ARDS was a common pathological mechanism of lung damage in SARS and MERS infections too. ARDS has been associated with an important immunopathological mechanism known as a cytokine storm. SARS and MERS patients showed rapid elevation of many proinflammatory cytokines and chemokines such as IL-6, TNF, IFN-γ, and CCL5 are known to cause the cytokine storm. Just like SARS and MERS, this cytokine storm activates violent immunological reactions in the lung tissue resulting in ARDS followed by multiple organ system damages in COVID-19 patients. COVID-19 patients were seen to elicit increased levels of numerous pro-inflammatory cytokines as well as chemokines such as IFN-g, IL-1b, MCP-1, and IP-10. Also, some severe cases of COVID-19 showed increased levels of G-CSF, TNF-α, and MIP-1A. Disease severity seems to correlate with the type of inflammatory cytokines found in COVID-19 patients. High levels of IL-2R and IL-6 seems to predict disease severity.
Immune evasion

Initial reaction by the immune system to the entry of viral particles is recognition of highly evolved viral structures called PAMPs via pattern recognition receptors (PRRs) of innate immune cells. SARS and MERS coronaviruses were seen to produce double-membrane vesicles that help escape this recognition, thereby allowing the replication of viral particles within these vesicles\(^\text{15}\). Likewise, both coronaviruses were seen to execute multiple mechanisms to interfere with signals leading to IFN-1 synthesis and hence further impede the downstream signaling cascade. These signal dampening strategies are known to be directly related to disease severity\(^\text{16}\). During the IFN-1 induction response, the SARS virus intrudes downstream signaling of RNA sensors either directly or indirectly. Indirect mechanisms include ubiquitination and degradation of RNA sensors and also by interfering with nuclear translocation. In addition to these mechanisms, the MERS virus uses additional strategies like modification of repressive histones. After the initial interferon secretion, SARS and MERS viruses were seen to become equipped with many mechanisms that interfere with interferon signaling\(^\text{17}\). Similar immune evading mechanisms might be employed by SARS-CoV-2 which might have resulted in its extremely increased contagiousness.

Two-phase immune response

Immune responses in COVID-19 infection are seen to be in two phases. In the incubation phase and initial stages, specific adaptive immune reactions are responsible for virus limitation and to prevent progression to severe disease. The general health status of the patient along with the absence of genes that led to increased susceptibility to infections plays an important role in the progression of the disease from mild to severe stages. However, the absence of any of the above factor would result in disease progression especially involving organs with high numbers of ACE-2 receptors and possibly other unknown receptors. This viral proliferation triggers innate immune response contributed mainly by pro-inflammatory cytokines such as IL-2, IL-7, IL-10, IP-10, MCP-1, MIP-1A, G-CSF and TNFα secreted by macrophages and neutrophils in the lungs. Severe lung damage along with multiple organ failure is the main reason of death in COVID-19. Once damaged, the lung epithelial cells regeneration could occur from the type I pneumocytes. After enough lung damage the innate immune response may not be very helpful instead may cause more damage. Hence, at this stage inflammation needs to be controlled to prevent further lung damage and disease progression\(^\text{20}\).

Mild vs severe disease

Comparing the distribution of various cellular compartments between control, mild and severe groups have been done. Increased proportions of T and NK cells were seen in the COVID-19 patients when compared with the control subjects. In comparison to mild cases, severe disease patients showed more macrophages and reduced the number of T and NK cells. Data indicates not only increased recruitment of immune cells in the lungs of COVID-19 patients but also the increased immune cells correlated positively with disease severity. With regards to macrophage recruitment, severe disease patients showed a greater number of differentiated macrophage populations in addition to primitive monocyte populations. With regards to the CD8+ lymphocyte population, mild disease COVID-19 patients showed initial rise attributing to disease limitation. But some severe COVID-19 patients also showed a rise in CD8+ lymphocyte population which is considered to be because of activation induced by increased inflammation or a delayed immune reaction to the infection in severe COVID-19 patients\(^\text{18}\).

The discrepancy between the severity of cases have been seen to vary between different geographical location might be because of antibody dependent enhancement (ADE) because of previous exposure to other types of coronaviruses probably local viruses. ADE manipulates the immune reaction resulting in severe disease such as sustained inflammation, decreased lymphocytes and cytokine storm\(^\text{19}\).

Disturbingly, even after being cured and discharged from hospital, some COVID-19 patients returned to viral positivity and few of them again became symptomatic. This shows that some cured patients did not develop adequate virus limiting immune reactions. This warrants the monitoring of all recovered patients. Also, these patients may not respond to vaccines that are under developing stages for COVID-19, since they
have difficulty in mounting an immune response against the viral particle. This phenomenon needs to be remembered while developing strategies for vaccines against COVID-19 infections.

**Immunosuppressed patients**

Logically, patients with transplants are expected to have worse outcomes in coronavirus infections such as SARS, MERS and COVID-19. But no known worsening case of SARS was reported in immunosuppressed patients.

Previous data on SARS and MERS along with recent reports on COVID-19 show no evidence of immunosuppression as a risk factor for virus acquisition in all three coronaviruses. No fatality or rise in morbidity and mortality has been attributed to immunosuppression in any form.

A recent report on the effect of cancer chemotherapy on COVID-19 patients seems to be largely related to other associated comorbidities more than cancer therapy itself.

**CONCLUSION**

Understanding of the immune status of COVID-19 patients must be attempted with all the available limited research data and known knowledge on other coronaviruses like SARS-CoV and MERS-CoV. This understanding must be remembered while devising and formulating strategies for development of vaccines and therapies for COVID-19 infection to enhance the outcome. This rapid mini review is an attempt at understanding the immune status of COVID-19 infected patients with reference to SARS-CoV and MERS-CoV viruses. This may help in follow up and vaccine development in very near future.

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