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Lymphocytes as Predictor of Severity in COVID19

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Abstract: ***The outbreak of the COVID-19 has led to various studies to determine the correlation between severity of the disease and decreased lymphocytes in patients of COVID 19. The increase in monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and marked increase in levels of cytokines, such as IL-2R and its ratio to lymphocyte count, correlated with severity of the disease and poor outcomes. Although the pathophysiology involved in COVID-19 has not yet been clearly known, an insight into the underlying mechanisms that lead to the observed lymphopenia can be helpful for understanding the disease pathogenesis and would help in better management of such patients. Here we briefly discuss the clinical significance of lymphopenia that sets in during the course of COVID-19 and the mechanism behind it to determine if these changes holds any significance to the prognosis, which would help us in understanding of the disease better and would lead to the discovery of new therapeutic options of the patients of COVID-19.***

Keywords: COVID-19, lymphopenia, disease severity, cytokines, therapeutic options

1. Introduction

The coronavirus disease (COVID-19), which is caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has hit the world in 2019. The first case occurred in Wuhan in China in December 2019 followed by which the virus spread all over the world. [1,2]. COVID 19 is rapidly spreading as a devastating global pandemic. Now after the third wave has hit the world, it is firmly believed that COVID-19 will only increase and so would be the increasing demand for intensive care. In such scenario identification of the critical patients plays a vital role for the better management of the disease. Now it becomes very important to prioritize health-care resources with proper triaging.

Studies done from the data obtained from severe forms of Middle East respiratory syndrome coronavirus and recent studies concerning SARS-CoV-2 shows that the response of the immunity of the host is major contributary factor for the pathogenesis of COVID-19(1,3). It revealed that for the control of viral infection, Cytotoxic T lymphocytes and natural killer cells plays a very vital role. An exhaustion of the antiviral lymphocytes is reportedly seen in patients of COVID-19. However, still there are limited evidence available for concluding the role of lymphocyte count in predicting the severity of COVID-19 (5).

In contrast the importance of B cells and anti-SARS-CoV-2 antibodies in the process of recovery of COVID 19 patients is fully understood. At the same time its is also believed that B cell activity may not be the only key for the recovery. A patient of multiple sclerosis affected by COVID-19, who was treated with ocrelizumab, an anti-CD20 B cell depleting antibody, was fully recovered after hospitalization of few days[4]. Another study showed two COVID-19 patients having X-linked agammaglobulinemia (XLA), which is found to be a rare genetic disorder resulted in a lack of mature B cells but showed complete recovery[5]. Pneumonia was developed in this patient but did not need intensive care or mechanical ventilation. Such studies have brought in limelight the importance of B cells involvement in a successful response in patients with SARS-CoV-2 infection. Another study revealed, in severe COVID-19 cases, antibody-secreting cells are higher in number than that in mild cases [6]. Numerous studies have shown that titers of virus-specific antibodies is directly proportional to the severity of the disease. The fact that these antibodies are protective or not, still remains unclear because studies on similar viruses have also shown two types of antibody response; one being neutralizing and protective, whereas other that can exacerbate inflammatory responses and can cause lung injury [7]. Therefore, it is very much possible for patients with severe COVID-19 having high antibody count may not mount an appropriate neutralizing antibody response, whereas patients who have recovered from COVID-19 may have predominantly protective-neutralizing antibodies. [8]. However, it needs further studies to clearly understand the significance of increased titers of antibodies in the pathogenesis of the disease in severe cases.

Therefore, here we hypothetically conclude the possible underlying reasons as the cause for lymphopenia in severe COVID-19 patients, most important being the decrease in the T cell counts:

- The inflammatory cytokine storm plays the vital role for lymphopenia seen in COVID-19 patients. Lymphopenia seem to closely correlate with the serum level of pro-inflammatory cytokines, such as TNF-α and IL-6, whereas normal levels of such cytokines are seen in patients who have recovered. Autopsy based studies which are done on lymphoid organs from patients who had succumbed to COVID19 revealed lymphocyte death massively, which was found to be due to increased levels of IL-6 and Fas-FasL interactions. When patients were treated with tocilizumab, an IL-6 receptor antagonist, it was found there was an increase in the number of circulatory lymphocytes, which further suggested IL-6 increase as the key factor in the development of lymphopenia. There has been another study suggesting a vital correlation between the levels of IL-6 in patients of COVID-19 and the impairment in the cytotoxic activity of T cells and NK cells [9]. Further studies are now needed for better understanding the relation of cytokine storm and the T and NK cell.
- Exhaustion of T cells is seen in COVID-19. A study revealed $CD4^+$ and $CD8^+$ T cells from COVID-19 patients had increased amount of cell surface expression of T cell immunoglobulin, programmed cell death protein 1 (PD-1) and mucin domain 3 (Tim-3), which are two markers of T cell exhaustion [10]. PD-1 and Tim-3 was found to correlate with the severity of the disease whereas another

study showed increased expression of NKG2A on T cell, another marker of $CD8^+$ T cells exhaustion, as well as decreased expression of some T cell activation markers, such as CD107a and IFN-γ. Thus, the regulatory T cells (Tregs) did not change in number in relation to the disease severity, which is suggestive of the fact that T cell exhaustion can occur in a process which is independent of Tregs. Therefore, studies are still needed for better understanding of relationship between the SARS-CoV-2 infection and T cells exhaustion.

- COVID-19 has the potential to cause T cell infection. Studies has showed that, MT-2 and A3.01 (two human T cell lines) having very low level of human ACE2 mRNA, the receptor from which it enters the host, can also be infected with the virus present in *vitro*. But at the same time the virus doesnot have the ability to replicate within the infected cells, as measured by qPCR expression of the viral N gene [11]. At the same time, a different study revealed that there was lack of expression of viral gene in patients with COVID-19, suggesting that there was no infection of the lymphocytes. [9]. This demands mor researches for better understanding of the fact that if any immune cell subsets can be infected, whether directly or indirectly.
- The SARS-CoV-2 virus is said to interfere with expansion of T cell expansion. A report suggested that there is downregulation in the genes involved in T cell activation and function, such as *MAP2K7* and *SOS1* in case of severe COVID-19. At the recovery time most of these genes usually return to normal levels [2]. This is probably the result of the tremendous change in the cytokine milieu in the due course of infection. Therefore, still further studies are required for a greater and detailed understanding on how activity of T cells and its proliferation are affected at the time of progression of the disease.

2. Conclusion

Therefore, decreased lymphocytes is a notable part of severe COVID-19. An increased level of certain cytokines, such as IL-6, and marked decrease in lymphocytes is directly propotional to the disease severity. In severe cases a prominent decrease in T cell counts is seen. Also, it is suggestive of the fact that immunosuppressive agents like Th1 cells, that suppress T cell response may be deleterious in fighting COVID-19, and hence should be avoided in premorbid patients with autoimmune diseases. More detailed studies are required in order to emphasize on pattern of lymphocyte changes in patients with COVID-19 to confirm and comment about the definitive predictive ability of lymphopenia in COVID-19.

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