Review article

Human Blood Cell Pathophysiology Associated with Acute COVID-19 Infection

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December 2019 marked the beginning of an outbreak of coronavirus disease (COVID-19 or SARS-CoV-2), which occurred in Wuhan City, Hubei Province, China. The most publicized effect of this virus is its impact on the human lungs, damaging the walls and lining of the air sacs causing respiratory symptoms, such as difficulty breathing and chest pain. This literature review highlights the changes in erythrocytes, leukocytes, and platelets during COVID-19 infections. Publicly available articles and reports related to COVID-19 infections on blood cell populations were collected and summarized. COVID-19 viral infections alter erythrocytic glycolytic pathways and membranes, and the ability to transport and deliver oxygen. T-cell lymphopenia is common among COVID-19 patients. The leukocytes produce excess inflammatory products during a "cytokine storm" where T and B lymphocytes, natural killer cells, neutrophils, and macrophages secrete pro-inflammatory cytokines to attenuate natural killer function to resolve inflammation. This further activates cytokine release from neutrophils and macrophages which, in turn, leads to exponential increase in inflammation, release of reactive oxygen species, superoxide anion, and nitric oxide, and associated tissue damage. With respect to platelets, thrombocytopenia has been observed in COVID-19 patients. The virus infects bone marrow cells resulting in abnormal hematopoiesis, direct destruction of platelets associated with the cytokine storm and immune function, and increased platelet consumption and tissue damage caused by the virus. The function of blood cell populations is severely compromised by SARS-CoV-2, contributing to severe disease outcomes, such as tissue and organ damage, and death. As more information is available about the virus, vaccines and the effect on erythrocyte, leukocyte, and platelet pathophysiology, this information will be used to develop new therapeutics to improve the recovery of patients from this disease.

Key words: COVID-19, SARS-CoV-2, erythrocytes, leukocytes, platelets

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third virus to have caused coronavirus-related outbreaks in humans over the past 20 years; following the severe acute respiratory syndrome (SARS) from 2002–2004 and in 2012 the Middle East respiratory syndrome (MERS).[1] Through comparing the different coronavirus species, it has been identified that SARS-CoV-2 is far more infectious, the overall number of deaths has far

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exceeded fatalities from SARS and MERS.[2] SARS-CoV-2 has caused a global pandemic of acute respiratory disease, namely the coronavirus disease 2019 (COVID-19), and its high transmissibility has made it a significant international health concern. Most of those infected will experience mild to moderate respiratory symptoms and will recover without special treatment. However, those with an underlying health condition (i.e., immuno-compromised) or the elderly, are more likely to become severely ill and may die from COVID-19. Many published studies and literature reviews have highlighted the respiratory symptoms associated with SARS-CoV-2 infection, while media coverage of the vaccines used to prevent COVID-19 infections has focused on the thrombotic issues caused by the vaccines. This literature review aims to explore and summarize the effects that the SARS-CoV-2 virus has on human erythrocytes, leukocytes, and platelet populations; and how their function is compromised by the SARS-CoV-2 virus and contributes to the disease symptoms and organ damage.

Effect of COVID-19 infections on erythrocytes

Erythrocytes, also known as red blood cells (RBCs), are the most common type of cell found in human blood, accounting for approximately 40% of the total blood volume. The main roles of RBCs are to transport gases including oxygen and carbon dioxide between the lungs and tissues. Therefore, disorders in morpho-physiology or function may result in tissue hypoxia and damage. In a recent review, researchers indicated that patients with COVID-19 infection present with abnormal red cell morphology with RBCs exhibiting the presence of anisocytosis, spherocytosis, stomatocytes, and polychromasia.[3] It has been demonstrated that hematological and morphological changes occur impairing RBC deformability post recovery from mild COVID-19 disease, stiffening the RBCs.[4] These changes coupled with alterations in hemoglobin, may also be associated with hypoxemia during COVID-19 infection. While Nader observed RBC aggregation as another crucial rheological parameter that is affected by acute severe COVID-19 disease.[5]

SARS-CoV-2 also affects RBC function by causing damage to the membrane proteins, which indirectly regulates their capacity to release oxygen and allows them to squeeze through capillaries. COVID-19 infections have an impact on the oxidation process of band 3 and binding with spike 1 protein (S1).[6] Alterations to the band 3 anion transport protein can result in changes to the ATP release mechanisms of RBCs, and thus, reduces vasodilation and oxygen delivery to tissues, causing hypoxia in patients. To further support this notion, analysis of the RBCs from COVID-19 patients was completed using real-time deformability cytometry. An anomaly in structure was observed, which was mainly characterized by the appearance of small RBCs with low deformation in typical channel flow conditions.[7] More specifically, the median deformation of the RBCs exhibited a weak decrease in COVID-19 patients compared with healthy donors and recovered patients. In addition, lipidemic analyses also observed that the membrane of the RBCs from infected persons had lower levels of short-chain fatty acids and increased long-chain saturated fatty acids.[8] Furthermore, as mature RBCs cannot synthesize new proteins to replace damaged ones, and the average lifespan of an RBC is 120 days, it was hypothesized that the circulation of irreversibly damaged RBCs with impaired functions contribute to the long-term effects of COVID-19.[8]

Researchers have also reported that the RBCs in those infected by the SARS-COV-2 virus showed significant alterations in glycolysis and more specifically exhibited elevated sucrose consumption.[8] This change in the glycolytic pathway in the RBCs of COVID-19 patients is likely due to infected individuals having higher levels of phosphofructokinase, an enzyme that

limits the rate of glycolysis. Another possibility is that SARS-CoV-2 in the human cell activates mitochondrial oxidative damage, which upregulates intracellular production of reactive oxygen species, which then increases cellular injury, intracellular stress, and increases the concentration of glucose in the infected cell. Consequently, cellular glucose metabolism becomes altered, changing the final product of the glycolytic pathway.[8] RBCs of COVID-19 patients also exhibit increased levels of glycolytic metabolites.[8] COVID-19 infection induced hypoxia affects 20% to 40% of patients and it was theorized that the increase in glycolytic metabolites was to counteract these effects. Glycolytic metabolites enhance the capacity of hemoglobin to off-load oxygen, thus providing sufficient oxygen to the tissues. However, this limited RBC capacity to readily respond to environmental variations in hemoglobin oxygen saturation causes some of the respiratory symptoms experienced by those with COVID-19.

Changes in leukocyte function with COVID-19 infections.

Leukocytes account for approximately 1% of a human's total blood volume and normal concentrations in human blood varies between 4,000 and 10,000 cells per microliter. Macrophages typically arise from bone marrow precursor cells, which develop into monocytes, and function to phagocytose pathogens, release pro-inflammatory cytokines, and antimicrobial mediators. Neutrophils are similarly produced in the bone marrow and rapidly respond to trap and remove invading pathogens. T cells mature in the thymus and mainly function to kill infected host cells, produce cytokines, and regulate the immune response.[9] T cell lymphopenia occurs when there is an abnormally low number of T lymphocytes in the blood. It is currently unknown as to why COVID-19 infection causes a decrease in T lymphocyte levels, but it has been suggested that the inflammatory cytokine storm is likely a key factor behind the observed lymphopenia.[10]

Previous studies regarding COVID-19 infection and the human immune system have noted that infection with SARS-COV-2 is accompanied by an aggressive inflammatory response in an event known as the "cytokine storm."[11] This involves the release of a large number of pro-inflammatory cytokines by cells including T and B lymphocytes, natural killer cells, neutrophils, and macrophages.[11,12] The cytolytic function of natural killer cells is diminished in some forms of the cytokine storm. This can lead to prolonged antigenic stimulation and difficulty resolving inflammation. Neutrophils produce an extracellular network of fibers that amplify cytokine production during the cytokine storm and macrophages can become activated and secrete excessive levels of cytokines, ultimately causing organ failure.[12]

Another consequence of the "cytokine storm" is the overproduction of pro-inflammatory cytokines, which is due to a loss of negative feedback in the immune system.[13] The main cytokines involved in the induced cytokine storm are interleukins 1 and 6, tumor necrosis factor alpha, colony stimulating factors, growth factors, and interferons. These cytokines exert positive feedback on other immune cells, including macrophages, neutrophils, and T cells; which are recruited to the site of infection in excessive levels, leading to the exponential increase of inflammation.[13] The increase in these three types of immune cells and the resulting exacerbation of the inflammatory process can produce destructive results on human tissue, which leads to the destabilization of endothelial cell to cell interactions, vascular barrier, and capillary damage.[11] In addition, increased cytokine production the release of reactive oxygen species, superoxide anion, and endogenous nitric oxide are induced; which all contribute to the myocardial damage experienced by some COVID-19 patients.[14] The cytokine storm is also associated with a downregulation of angiotensin-converting enzyme 2 receptor (ACE2), which leads to an increase in angiotensin II and stimulation of angiotensin II

receptor type 1 (AT1R). This is believed to be the causative factor for severe lung complications in several COVID-19 cases. However, at this stage, the driver of the cytokine storm in COVID-19 patients is unknown.[12]

Effect of COVID-19 infections on platelet function

Human blood contains 150,000 to 400,000 platelets per cubic millimeter. Thrombocytopenia is a condition affecting those with an abnormally low platelet count. A study involving 1,099 patients from 31 provinces/direct-controlled municipalities in China showed that 36.2% had thrombocytopenia, suggesting the possibility that COVID-19 infections interfere with the platelet count.[15] The possible mechanism of thrombocytopenia in COVID-19 patients involves multiple theories. First, SARS-CoV-2 infections may directly reduce platelet production causing thrombocytopenia. Coronaviruses can infect bone marrow cells and cause abnormal hematopoiesis through receptors such as the aminopeptidase N (CD13) receptor, which decreases the production of platelets. This receptor removes the N-terminal amino acids from unsubstituted oligosaccharides, allowing it to regulate the activity of hormones, cytokines, and chemokines; which take part in inflammation.[16] This theory is further supported by others who speculated that after being impacted by the cytokine storm induced by COVID-19 infection, the hematopoietic progenitor cells in bone marrow are destroyed, thus decreasing platelet production.[17] The second possible reason as to why thrombocytopenia occurs is due to the possibility of COVID-19 infection increasing platelet destruction.[15] COVID-19 infection increases the levels of autoantibodies and immune complexes, resulting in destruction of platelets by the immune system. This is due to the production of antibodies which bind to antigens on platelets through molecular mimicry. The third possible hypothesis is that COVID-19 infections may increase platelet consumption, as being infected leads to damaged lung tissues and pulmonary endothelial cells, and hence, there is an increased utilization of platelets.[18]

COVID-19 infections have also been found to alter gene expression in platelets, as well as platelet-specific granule content. Two-related genes, S1000A8 and S1000A9 are upregulated in the platelets of COVID-19 patients, resulting in the increased production and release of myeloid-related proteins 8 and 14, which activate endothelial cells to promote an inflammatory hypercoagulable state. Platelet membranes contain $P2Y_{12}$, a Gi-coupled receptor expressed on platelets, which regulates ADP-induced platelet aggregation. At the same time $P2Y_{12}$ receptor activation contributes to the inflammatory process. This suggests that targeting the adenosine diphosphate receptors $P2Y_{12}$ on the platelets in COVID-19 patients may reduce proinflammatory platelet-endothelial interactions.[19] The myeloid-related proteins activate endothelial cells, promoting an inflammatory hypercoagulable phenotype, which leads to higher levels of clotting and inflammation in vessels, and hence, greater disease severity.

Researchers have also determined that platelet-specific granule content levels are elevated in patients and linked to increased platelet activation, resulting in platelet hyperactivity in severe COVID-19 cases. Other gene-expression changes that occur in platelets from COVID-19 patients involve pathways associated with protein ubiquitination, antigen presentation, and mitochondrial dysfunction, which increases platelet activation and aggregation that was caused by increased mitogen-activated protein kinase pathway activation and thromboxane generation. As such, COVID-19 infection is associated with platelet hyperreactivity, which may contribute to COVID-19 pathophysiology.[20]

Conclusion

The current COVID-19 pandemic is a highly contagious pathogenic viral infection which has become an international public health problem. Infected persons may be asymptomatic or suffer from mild to severe symptoms,

including fever, coughing, and diarrhea. There have been rapid advances in the world's understanding of the SARS-CoV-2 pathogen, clinical characteristics of COVID-19 infection, and development of COVID-19 vaccines. This literature review highlights the impact of SARS-CoV-2 infections on blood cell populations and how they can contribute to the pathophysiology of the disease.

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