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Hematological Findings in COVID-19 and Insights to Stem Cell Therapy: From Bench to Practice

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Abstract

Context: As the COVID-19 was spreading to all countries, its manifestations were identifying gradually, which were related to several organs.
Evidence Acquisition: COVID-19 is associated with distinct hematological changes, increased serum inflammatory markers, and coagulopathy. Most of these changes are related to the patients' prognosis and mortality, particularly in those with severe disease.
Results: Firstly, we discussed the associations between COVID-19 clinical features and complications, and secondly, its hematological findings and coagulopathy are investigated.
Conclusions: Such associations not only may shed light on our prognostic view of patients with COVID-19 but also will entail significant therapeutic implications. One of its key implications is to utilize the mesenchymal stem cells (MSCs) to treat patients with COVID-19. Herein, this kind of novel therapy will be discussed, as well.

Keywords: COVID-19, Hematological, Immunology, Lymphocytes Prognosis, Mesenchymal Stem Cells

1. Context

The coronavirus infection, known as COVID-19, was first presented as an outbreak of atypical Pneumonia in late 2019 (1). Since then, it has spread globally to infect over 9 million cases, by the end of June 2020 (2). This pandemic has impacted health and the economy worldwide on an unprecedented scale. As the pandemic sweeps all over the world, clinicians started to realize that COVID-19 has important systemic manifestations, including affecting many systems of the body, including the cardiovascular, endothelial, and immune systems. Indeed, COVID-19 is associated with distinct hematological changes, increased serum inflammatory markers, and coagulopathy. More importantly, most of these changes are related to the patients' prognosis and mortality, particularly in those with severe disease. While we are learning constantly about the changing epidemiology, the rapidly evolving underlying science, together with insights from previous coronavirus infections, such as SARS and MERS-COV, can help us to better understand COVID-19 and its diagnose and treatment.

In this article, firstly, we discussed the associations between COVID-19 clinical features and complications, and secondly, its hematological findings and coagulopathy are investigated. Such associations not only may shed light on our prognostic view of patients with COVID-19 but also will entail significant therapeutic implications. One of the key implications is to utilize the mesenchymal stem cells (MSCs) to treat patients with COVID-19. Herein, this kind of novel therapy will be discussed, as well.

2. Evidence Acquisition

2.1. COVID-19 Virology

The COVID-19 pandemic is caused by a novel beta coronavirus that has a 80% similarity with the previous coronavirus, which caused SARS outbreak in 2003 (1). However, the novel virus had acquired many features that changed its efficiency, which translated into more aggressive. The 3D structure of the new COVID-19 binding site is more compact, has more binding capacity, and has a potentially en-

hanced binding affinity to its receptor, the ACE-2 (3). Another distinct feature of the SARS-CoV-2 is its furin cleavage site inserted at the spike S-protein subunits (4, 5), which characteristically enhances the virus' ability to internalize into affected cells.

The SARS-CoV-2 internalization receptor causing COVID-19 has been confirmed to be the ACE-2 (4, 5), in harmony with the cell TMPRSS2 membrane protease that primes the spike S protein of the virus to facilitate its entry into the cell (6). ACE-2 is the same functional receptor of the earlier SARS-CoV-1. However, in the absence of TMPRSS2, the viral infectivity is not enhanced (6). In vitro experiments showed that protease inhibitors against TMPRSS2 appear to block effectively viral entry and infection of lung cells.

Interestingly, it was observed that ACE-2 has important immune-modulatory actions. ACE-2 can directly interact with macrophages in the setting of vascular and lung inflammation, as demonstrated by genetic manipulation in a model of SARS, as well as by the salutary anti-inflammatory effects of infusion of recombinant ACE-2 (7). Indeed, ACE-2 effectively reduces the levels of angiotensin II, which is a direct pro-oxidant and pro-inflammatory. Therefore, ACE-2 is important in controlling excess systemic inflammation in the presence of danger signals (7).

As TMPRSS2 and ACE-2 facilitate SAR-CoV-2 entry, the co-presence of these two important molecular entities in tissues can explain the tropism of viral proliferation. TMPRSS2 and ACE-2 are co-expressed in the lung, heart, liver, kidney, gut smooth muscle, neurons, and immune cells. Their distribution may help to explain the patient's clinical presentation and/or the characteristic laboratory findings in COVID-19. Interestingly, circulating ACE-2 levels in patients are sex-dependent, being 50% higher in males than in females with heart failure (8, 9). Another intriguing association is the fact that in COVID-19 infections, after adjustment for differences in risk factor profiles, the death rate of males is much higher than that of females (9).

During virus engagement of the ACE-2 receptor in the presence of TMPRSS2, the virus can enter the target cell through endocytosis or membrane fusion. The positive-strand viral RNA is then transcribed by the host cell ribosome while it is simultaneously transported to the endoplasmic reticulum to mediate transcriptional activation and production of viral component proteins. These are ultimately assembled into intact viruses and discharged from the cell. This process can disable or damage the host cell, leading to the release of potentially harmful signals to activate the body's innate immune responses. Implementing this virus-receptor interaction into clinical practice may provide many opportunities for potential intervention, and a number of therapeutic trials are currently ongoing. Infusion of recombinant human ACE-2 may act as a decoy to interfere with viral replication. Hydroxychloroquine or chloroquine may interfere with cellular endocytosis of the virus, and viral proliferation can interfere at multiple stages. One of them is the inhibition of RNA polymerase with remdesivir (9).

3. Results

3.1. Clinical, Laboratory, Hematological, and Immunological Findings

According to the evidence, COVID-19 patients may present several clinical scenarios, ranging from asymptomatic carriers to those affected by a severe acute respiratory infection (SARI) (10), leading to severe lung affection and impairment, which may be complicated by an exaggerated systemic inflammatory response, cytokine-storm, and even death (10). Also, there is a wide spectrum of symptoms ranging from acute febrile illness with body aches and malaise to cough and shortness of breath. Interestingly, with time, other early systems were identified, affection (for example) gastrointestinal system (e.g. loose motions) or neurologic (e.g. headache and delirium) (11). Pulmonary symptoms may develop into severe pneumonia characterized by progressive shortness of breath, tachypnea, and hypoxemia (12).

Probably several factors contribute to these differences in clinical presentations, including the age of the patient, the degree of viral load, host immune response, and the presence or absence of co-morbidities. As per published recent data, there are 5 clinical phenotypes of COVID-19, which have distinct clinical presentations, prognostic features, and consequently, different management strategies (13). Consequently, these different phenotypes can lead us to question the concept of, are we in need of "phenotype-based tailored management"?

In the diagnosis of SARS-CoV-2 infection, it is important to pay attention to laboratory abnormalities, which reveal characteristic changes in the blood picture (lymphopenia and thrombocytopenia) as well as increased levels of lactate dehydrogenase and d-dimers (9, 14).

Whatever the purpose of performing laboratory testing in COVID-19 patients (i.e., either routinely for diagnostic purposes or prognostically for research purposes), definitely they have improved our understanding of this "new disease". The serum levels of different cytokines were studied in patients with COVID-19 and compared between severely ill patients admitted to the intensive care unit (ICU) with milder non-ICU ones. ICU patients had higher

levels of IL-2, IL-7, IP-10, MCP1, MIP1A, IL-10, GSCF, and TNF-α (14). Notably, this increase in proinflammatory cytokines was associated with pneumonia and extensive lung damage (15).

Interestingly, the "cytokine-storm" observed in severe COVID-19 has several similarities with the four entities of what is called "hyper-ferritinemic syndrome". These entities include adult-onset Still's disease (AOSD), macrophage activation syndrome (MAS), catastrophic anti-phospholipid syndrome (CAPS), and septic shock. It is believed that COVID-19 systemic inflammation is tightly related to these syndromes. This common pathogenic background has led scientists to try the use of therapies that target such inflammatory mediators. Hence, some clinical trials are addressing the efficacy of IL-1 and IL-6 inhibition by Anakinra and Tocilizumab, respectively (16).

In parallel with the SARS-CoV-1 infection, in which lymphopenia was also observed to be highly prognostic, reports of SARS-CoV-2 infections had shown an early reduction in T cells, particularly a reduction in CD4+ more than CD8+ T cells (17), then recovery of lymphocyte count coincided with clinical improvement.

The important role of CD4+ T cells was further delineated in a primary infection model with SARS-CoV in senescent mice, which indicated that CD4+ T cells could enable the production of neutralizing antibodies and a balanced immune response. Without CD4+ T cells, there was much more severe interstitial pneumonitis. When both CD4+ and CD8+ T cells were depleted, there was a predominance of neutrophils and innate immune macrophages (18). Accompanying the loss of CD4+ T cells, there was an unusual macrophage predominance in SARS-related lung infiltration. This can be accompanied by hemophagocytosis in the lung and spleen, compatible with severe immune cytokine dysregulation (19). Prolonged virus shedding in many individuals is considered as another indication that SARS-Cov-2 induces a relatively mild immune response. Virus proliferation is extremely rapid in COVID-19 patients, yet many patients are asymptomatic, which suggests that while the immune system is mounting a response, it is not adequate to attenuate viral replication potential.

Dynamic changes in the peripheral lymphocyte subset seem to play a role in patients with COVID-19. There are reports of decreased levels of CD4+, and CD8+ T cells, natural killer (NK) cells, and total lymphocytes in patients with COVID-19, notably severe cases had lower levels than mild ones (19). Moreover, there was a significant association between the CD4+/CD8+ ratio and the inflammatory status. With post-COVID-19 therapy, 67% of patients showed an improved response, with a subsequent increase in B cells and CD8+ cells. The importance of these dynamic changes came from the observation that post-treatment could decrease CD8+ T cells and B cells and/or increased CD4+/CD8+ ratio, as significant independent factors of poor efficacy (19).

With regards to thrombocytopenia, a recent meta-analysis has suggested that the severity of the COVID-19 disease is closely related to thrombocytopenia (14).

Importantly, several studies have shown that the lethal myocardial injury, which may happen among hospitalized patients with COVID-19, is closely related to marked thrombocytopenia.

3.2. Vascular Endothelium, Thrombosis, and Coagulopathy

As ACE-2 is also expressed by endothelial cells, together with observations found in patients with COVID-19 (e.g., thrombosis, kidney disease, pulmonary embolism, and cerebrovascular and neurologic disorders), this indicates that the virus is targeting one of the most important organs in the human body (i.e., the endothelium) (19, 20).

Back to physiology, if the endothelium loses its physiological properties, then endothelial dysfunction status is reached in which there is a tendency to promote vasodilation, fibrinolysis, and anti-aggregation (19, 20). It's well proved that higher mortality in patients with COVID19 is due to the presence of clotting disorders, with organ dysfunction and coagulopathy (20). Analysis of coagulation profiles of COVID-19 patients revealed interesting findings. Non-survivors had significantly higher levels of fibrinogen degradation products (FDP) and D-dimer, as well as longer prothrombin time (PT) than those who survived (21-23). Moreover, during the late stages of hospitalization, the clinical diagnosis of disseminated intravascular coagulation (DIC) was observed among non-survivors (21-23).

A dysregulated immune response, which is observed in COVID-19 patients, plays a crucial role in endothelial dysfunction and thrombosis. Endothelial cells represent one-third of the lung cell population. Thus pulmonary endothelium represents an essential barrier between the blood and interstitium. Therefore, it is not surprising to find that pulmonary endothelial damage is the hallmark of ARDS (23-25).

Increased vulnerability of patients with cardiovascular disease (CVD) and/or diabetes mellitus to COVID-19 may be explained by the cytokine storm, which leads to an abrupt deterioration of the inflammatory response and hypercoagulation. The inflammatory response among the latter might be the iceberg of an underlying chronic inflammation (21, 26).

As proved before, as a cause of clinical deterioration in viral pneumonia, acute pulmonary embolism (PE), is reported frequently in COVID-19 patients (21, 23). Again, en-

dothelial dysfunction is the cornerstone pathogenetic factor in hypertension, thrombosis, and DIC; all of them are common risk factors for COVID-19, as well (21, 23). Clinical implications for these observations denote that it is important to select those patients with COVID-19 at higher risk of thromboembolic disease and practice diagnostic workup that leads to the early diagnosis of pulmonary thromboembolism; definitely this will improve the outcomes of patients with COVID-19 (21, 27, 28).

A group of recently published articles has investigated autopsy studies of COVID-19 patients. Ackermann et al. (29) examined the histologic pattern of diffuse alveolar damage, combined with perivascular T-cell infiltration. The lungs of COVID-19 patients presented severe endothelial injury, characteristically with the presence of the virus intracellularly. The pulmonary vessels showed widespread thrombosis with microangiopathy (29). In a study from the USA, autopsy findings confirmed that COVID-19 is a systemic disease with major involvement of important organs (30). The authors' findings in severe COVID-19 disease were reflections of direct viral-induced injury of multiple organs, on the background of marked procoagulant state, thrombosis, and coagulopathy.

Based on these pathophysiologic findings in patients with COVID-19, assessment for the risk of venous thromboembolism (VTE) in hospitalized COVID-19 patients is an emerging issue. Those patients do commonly have risk factors for VTE. Some of these factors include prolonged immobilization during hospitalization, aging, underlying chronic inflammation with the iceberg of an acute inflammatory state, the presence of other cardiovascular risk factors (i.e. hypertension, diabetes, obesity), and/or CVDs (27, 28, 31). Adding to these factors, we should not forget mechanical ventilation, prolonged ICU stay, central venous catheterization, the use of multi-medications, and surgery, all of these may induce damage to the vascular endothelium. The combination of all these factors may lead to deep venous thrombosis (DVT) or even lethal pulmonary embolism (PE). Thus, it has been recommended that VTE risk assessment should be performed for all acutely ill hospitalized COVID-19 patients, and the strategy of employing thromboprophylaxis should be implemented for all high-risk patients according to the relevant clinical practice guidelines (31, 32). The use of risk assessment models (RAM) such as IMPROVE-VTE might be of help. It has been recently shown that modified IMPROVE-VTE RAM, which includes the D-Dimer levels together with other clinical predictors of VTE, could enhance our stratification of high VTE risk in COVID-19 patients candidate for thromboprophylaxis (33). Possible drug-drug interactions with a concomitant antiviral (e.g., ritonavir) and antibacterial (e.g., azithromycin) therapies support the use of low molecular weight heparins (LMWH) or unfractionated heparin (UFH) over direct oral anticoagulants (DOACs) (33).

3.3. Mesenchymal Stem Cells as a Potential Therapeutic Option for COVID-19

Stem cells are a population of precursor cells characteristically capable of differentiation into many different body cell types. Stem cells are unspecialized cells that can give rise to specialized ones, and they have the ability to divide and renew themselves for long periods, as well. Based on their source, stem cells can be divided into embryonic, fetal, adult, cord blood, amniotic fluid, and induced pluripotent stem cells (34).

Stem cells have been applied in many fields, including tissue engineering, understanding of cancer biology, drug screening, therapy of several incurable ailments, animal biotechnology, testis xenografting, and spermatogonial stem cell transplantation. Stem cells have two important distinguishing features; A, they are unspecialized cells with the ability of self-renewal through cell division, even after long periods of inactivity; and B, under certain conditions, they can differentiate into tissue- or organ-specific cells with special functions. Interestingly, stem cells have the ability to become more than 200 different cell types in the body (35).

Stem cell therapy is a treatment modality that utilizes stem cells, or cells derived from them, to replace/repair damaged cells or tissues. The general principle of stem cell therapy is to take the advantage of the natural ability of the human and animal body to heal tissues by regeneration. Typical utilization of stem cell therapy involves direct injection or cell seeding (cell + scaffold) and transplantation of a graft. It may be applicable to utilize stem cell therapies for major disease entities such as heart disease, neural defects, bone or connective tissue disorders, and hematological disorders (34, 35).

According to the previous studies, there are three main therapeutic strategies for using stem cells; A, stimulation of endogenous stem cells using cytokines, growth factors, and second messengers that can induce self-repair of damaged tissues or organs; B, Direct administration of stem cells, as they can differentiate at the nonfunctional tissue sites; and C, Transplantation of cells or tissues obtained from cultures of stem cell-derived differentiated cells (34, 35).

Support to the potential use of MSCs in treating COVID-19 patients came from experiences that MSCs have been identified to efficiently cure those infectious and noninfectious causes-induced acute respiratory distress syndrome

(ARDS) (36). The interesting MSCs immune-regulatory potentials rely upon modulating activation and efficiency of potent immune cells, suppressing lung inflammation, and enhancing the resolution of non-cardiogenic pulmonary edema (37).

Back to physiology, MSCs can efficiently influence the behavior of both innate and adaptive immune cells. They can release keratinocyte growth factor, prostaglandin E2, IL-6 and IL-13, granulocyte-macrophage colony-stimulating factor, 3 to facilitate the phagocytosis and alternative activation of alveolar macrophage, decrease the release of interferon γ from natural killer cells, and modulate the cytokine profile of dendritic cell subsets. The IL-10, tryptophan catabolizing enzyme indoleamine 2, 3-dioxygenase, and transforming growth factor β (secreted from MSCs) can suppress the proliferation of T cells (38). Moreover, important properties of B cells like proliferation, differentiation, and chemotactic features can be efficiently impaired by MSCs, as well (39). Interestingly, all these important above-mentioned functions might also be effective on COVID-19-induced ARDS (CARDS).

Our previous experience with the therapeutic effects of MSCs on ALI/ARDS and graft -versus- host disease (GVHD), provides promising proofs for the application of MSCs on other ALI/ARDS, like CARDS. Furthermore, it has been observed that MSC treatment significantly improved H9N2 avian influenza- and H5N1-induced ALI/ARDS, indicating a promising efficacy of MSCs on viral ALI/ARDS (40-42). Importantly, MSCs may cure patients with the disappointing refractory ARDS, who failed to improve after mechanical ventilation and even extracorporeal membrane ventilation (ECMO), denoting that MSCs could be used for serious viral ALI/ARDS (43).

It is believed that the best role for starting MSCs therapy in the treatment of COVID-19 patients comes at the stage of those with "cytokine storm". Probably, MSCs therapy -via their reparative properties- can prevent the storm release of dedicated cytokines and, more importantly, promote endogenous repair (44).

In systemic infusion of MSC, part of the MSC population is entrapped in the lung, which is considered as a limitation. But in the case of COVID-19, it is rather an advantage, as these MSCs could recover the pulmonary microenvironment, protect alveolar epithelial cells, combat post-COVID-19 pulmonary fibrosis, and fight against disabling lung dysfunction, all of which are pathophysiologic characteristics of COVID-19 pneumonia (41-46).

Recently, many countries, including China, the USA, and Iran, have begun the promising approach of cell-based therapy. Recently, a Chinese pilot study, of patients with severe COVID-19 who received MSCs, is published. The study reported that patients were recovered and discharged (44). According to the results of these initial clinical trials and the global widespread of COVID-19 pandemic, we think that it is time to test the safety and efficacy of MSC transfusion in patients with COVID-19, especially for those with a severe or critical illness.

There are innumerable advantages in using MSC therapy in comparison with other therapeutic modalities, including: 1- Their easy accessibility and isolation from various available tissues such as bone marrow and adipose tissues; 2- They are multipotent stem cells; 3- MSCs can be stored for repetitive therapeutic usage; 4- They are easily expandable to significantly clinical volumes in a suitable period; 5- Clinical trials of cell-based therapy so far haven't shown adverse reactions to allogeneic MSC; and 6- Their safety has been documented in several world-wide clinical trials (43-45).

However, despite all these advantages, some issues remain to be solved, particularly those related to ethical issues, immunogenicity, and limited cell source.

Finally, while scientists are trying and waiting for the development of a vaccine(s) for COVID-19, as well as developing different therapeutic approaches to treat this horrible disease, it seems that MSCs-based therapy can be an ideal solution. Clinical trials for this cell-based approach, alone or in combination with other therapeutic modalities, are urgently needed to manage and improve the outcomes of COVID-19 patients, particularly those with severe disease.

4. Conclusions

COVID-19 is associated with distinct hematological changes, increased serum inflammatory markers, and coagulopathy. Most of these changes are related to the patients' prognosis and mortality, particularly in those with severe disease. There are links between COVID-19 clinical features and complications and its hematological findings and coagulopathy. These links can help clinicians to better understand the pathobiological mechanisms implicated in this novel disease. Moving from bench to practice is of crucial importance to scientists working in this field. The use of mesenchymal stem cells to treat COVID-19 patients seems to be a promising approach. Further studies are needed to clarify more clinic-pathologic links in COVID-19 that might improve outcomes of COVID-19 patients.

Footnotes

Authors' Contribution: SM, GA, NA, developed the idea, and all authors made a substantial contribution to the de-

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