Severe Cases of COVID-19 and High Association with Causes of Immune Dysregulation: A Systematic Review

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ABSTRACT: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for coronavirus 2019 (COVID-19), which was declared a pandemic in March 2020 by the World Health Organization due to the rapid spread representing a global health crisis. The disease is characterized by a wide clinical spectrum ranging from asymptomatic forms until severe viral pneumonia, which can evolve to severe acute respiratory syndrome, especially in elderly patients and/or with comorbidities. An efficient assembly of the immunological response of the patients becomes fundamental against SARS-CoV-2 infection and it has been demonstrating a significant relationship between severity of the disease and expression profile of the immune cells and the levels of pro-inflammatory cytokines. This review aims to present the main immunological mechanisms developed during the infection by SARS-CoV-2 in the evolution of the severe cases of COVID-19. The immune dysregulation of the Th1 cellular response standard, the instability in the production of neutralizing antibodies by plasma B cells, the difference in tropism of CD8+ T cells against virus proteins in early infection, late infection and reinfections, dynamic of alveolar macrophages and pulmonary innate lymphoid cells (TCR γδ) of the natural immune response and the high level of pro-inflammatory cytokines can determine the main cause of breath tissues damages and, consequently, a greater severity of the disease. Therefore, a complete understanding of the main immunological changes involved in SARS-CoV-2 infection can identify possible biomarkers in the evaluation of early prognosis of the severe cases of COVID-19, making possible better therapeutic success to the patients.

KEY WORDS: COVID-19, SARS-CoV-2, immune dysregulation, severe COVID-19

I. INTRODUCTION

The recent emergence and rapid global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease 2019 (COVID-19) poses an unprecedented health crisis that was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 and continued to aggressively spread across the globe infecting more than 3 million confirmed cases.1 SARS-CoV-2 was identified in December 2019 after sequencing clinical samples from a cluster of patients with pneumonia in Wuhan, China.2

COVID-19 causes a wide spectrum of clinical manifestations, ranging from asymptomatic or paucisymptomatic forms (with cough, fever, myalgia, and malaise) to full-blown viral pneumonia, which can lead to acute respiratory distress syndrome (ARDS).3 About 8–19% of patients, with the elderly and those with underlying comorbidities, particularly cardiovascular disease, diabetes mellitus, chronic pulmonary disorders or renal disease are especially at risk.4

As the pandemic progresses, the immunopathology of COVID-19 is becoming clearer, it has been reported that COVID-19 is associated with immunodeficiency and hyperinflammation manifested by a cytokine storm.5 Based on the knowledge generated from previous coronavirus data, and the recent studies on SARS-CoV-2, the present work aims to fill a space still little explored about the immunological mechanisms during the infection by SARS-CoV-2,
especially immune responses to severe acute respiratory syndrome.

II. IMMUNE RESPONSE IN SARS-COV-2

SARS is an infectious disease that posed a major threat to international public health in 2003, being identified as the causative agent of coronavirus (SARS-CoV), which are groups of viruses associated with the family Coronaviridae already known since the mid-1960s. Human respiratory system is the mainly target to these viruses can to cause a serious lung inflammation, renal and cardiac injury, mainly associated to patients with older age, immunodeficiency, sedentary, malnourished or that presents others comorbidities.

An efficient immune response is considered fundamental against SARS-CoV-2 and various studies have shown a significant relationship between the disease severity and the levels of proinflammatory cytokines and immune cells parameters. These data suggest that during COVID-19 evolution, the immune dysregulation and the high level of proinflammatory cytokines could determine the main cause of tissue injury.

The increased inflammation caused by SARS-CoV-2 and the consequent tissue damage are stimulated by hypersecretion of pro-inflammatory cytokines as interleukin-1 (IL-1), tumor necrosis factor alpha, IL-6, IL-1β and C reactive protein and the recruitment of proinflammatory macrophages, lymphocytes and granulocytes. The referred cytokines modifications is known as cytokine storm and will be better described at isolated one topic.

Levels of lymphocytes and subsets of T cells that play a significant role in the balancing of immune response varies according to the type of the virus due to possible viral pathologic mechanism. Recent studies have suggested that SARS-CoV-2 infection can lead to immune dysregulation through decrease of T cells. Most COVID-19 patients, especially in severe ones, presents a prominent lymphopenia that indicate a classical impairment of immune system.

The level of helper T cells, cytotoxic suppressor T cells and regulatory T cells are below normal level and in severe patients are even smaller when compared nonsevere cases. In Fig. 1, we demonstrate the initial interaction and activation mechanism of cellular immune response from CD4+ T and CD8+ T lymphocytes after SARS-CoV-2 infection and antigen presentation.

The immune homeostasis stimulated by regulatory T cells also presents decreased and, consequently, with lower activation, proliferation, and proinflammatory function of most lymphocytes including NK cells and B cells.

The immune reactivity pattern for CD4+ T cells in SARS-CoV-2 presents differences in comparison with SARS-CoV about interaction between cells receptors and surface viral protein. Spike, membrane (M) and nucleocapsid (N) viral proteins are clearly co-dominants for all cases in reactivity to SARS-CoV-2, while only Spike protein accounted for nearly two-thirds of reactivity in SARS-CoV with limited reactivity or no reactivity to M and N proteins.

On the other hand, cytotoxic response by T CD8+ cells the reactivity pattern to SARS-CoV-2 do not stimulated by Spike proteins, but M protein was the more strongly recognized beyond other antigens.
as N protein, which comprised nearly 50% of this total response.26

These data suggest that COVID-19 vaccines also must to be directioned to different CD4+ T cells and CD8+ T cells reactivity pattern responses against the SARS-CoV-2 proteins that may drive severe, moderate and mild responses of this infection.27

Cytotoxic immune response of the NK cells also are seen in lower expression in critically ill patients due, probably due to NK cell sequestration into target organs as the lung.29,30 However, it is unclear at this time if this decrease is due to NK cell redistribution in infected sites or cell death.

The antibodies production by B lymphocytes is considered as one of the main defense phases of the immune response being known like humoral response. The most people infected with SARS-CoV-2 display an rate antibodies time seroconversion between 10 and 14 days after infection. In some mild cases, detection of antibodies requires a more long time after symptoms and in a small number of cases, antibodies are not detected at all.28 These humoral dynamic can be associated by the quantitative reduction of B cells in COVID-19.29 Figure 2 shows humoral immune response activation to SARS-CoV-2.

It is likely that protective mechanisms through other arms of the immune response as memory and cytotoxic T cells, may alter the COVID-19 disease course upon reinfection either by diminishing symptoms in the absence of protective antibodies or by enhancing infection at the nadir of the humoral immune response by sub-neutralizing antibody titres.28

Alveolar macrophages (AMs) maintain lung homeostasis through clearance of dead cells, and invading pathogens. The lung harbors two distinct populations of macrophages, the that arise mostly from fetal liver monocytes and the interstitial macrophages (IMs), which are located with dendritic cells and lymphocytes in the interstitium.31

Higher numbers of monocytes/macrophages were identified in bronchoalveolar lavages samples from patients with severe diseases in COVID-19 and the profiles inflammatories monocytes found presented pro-fibrosis differentiation stage more so in severe than in mild COVID-19.32 The monocytes change profiles will be better explored below.

Innate lymphoid cells are particular lymphoid cell types as (ILCs) that are implicated in promoting diseases tolerance.33 SARS-CoV-2 viral load does not discriminate symptomatic from asymptomatic infection,34 and this discrepancy between viral load and severity of COVID-19 can be observed in infected children, who rarely manifest severe COVID-19,35 but may present viral loads as high as very sick adults.36 These observations indicate that disease tolerance mechanisms by ILCs can influence, directly, the severity of COVID-19.37

It is known that the equilibrium between the naïve T cells and memory T cells is fundamental for mediating the efficient immune response.38 Severe cases of COVID-19 shows an imbalance in these cells with higher naïve helper T cells relative values while to memory helper T cells decreased.20,23

The immunological events of high production of cytokines and activation of adaptative immune cells are parts of try to control the viral replication and to limit the spread of virus that is developed by inflammation response by body39,40 being
compromised, mainly, individuals that presents immunodepression.

III. HYPER-INFLAMMATION AND CYTOKINE STORM IN COVID-19

Hyper-inflammation in COVID-19 is related as one of more important cause to severe cases. It is possible that increased viral load promotes higher inflammation and severe cases trigger an inappropriate host response. Airway viral infections enables that epithelial cells, human peripheral blood monocyte-derived macrophages and dendritic cells promotes induction elevated levels of proinflammatory cytokines and chemokines, belatedly.

Cytokines play an important role in immunopathology during viral infection and innate immune response is the first line of defense against viral infection, however, dysregulated and excessive immune responses may cause immune damage to the human body.

In COVID-19, the inflammatory cytokine storm is closely related to the development and progression of acute respiratory distress syndrome (ARDS), presenting high serum levels of cytokines Th1 immune response and increase of mortality rate, configuring, in this way, an important factor which determines the clinical course of extrapulmonary multiple-organ failure seen in some COVID-19 patients without respiratory failure, suggesting that the inflammatory cytokine storm is the main cause of these injuries.

Studies have associated severe cases with a cytokine storm activated by recognition between virus protein and Toll-like receptors (TLRs) that initiate a cascade of events to the activation of the JAK-STAT and AKT/PI3K pathways (Fig. 3).

Th1 immune response is a key event in the activation of specific immunity, however, unlike SARS-CoV infected patients, patients with COVID-19 also have elevated levels of Th2 cell-secreted cytokines (such as IL-4 and IL-10), which inhibit the inflammatory response. The serum levels of IL-2R and IL-6 in patients with COVID-19 are also strongly correlated with the severity of the disease.

Initially, cytokines and chemokines profile in SARS-CoV immune response occurs in respiratory epithelial cells, dendritic cells (DCs), macrophages at the early stage and later secrete lower levels of the antiviral factors as interferons (IFNs) and up in levels of proinflammatory ILs as IL-1β, IL-6, and tumor necrosis factor (TNF) and chemokines [C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5].

In SARS-CoV-2, retrospective analysis of studies in patients with COVID-19 demonstrated increase to initial plasma levels of IL-1β, IL-1RA, IL-7, IL-8, IL-10, IFN-γ, monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte colony-stimulating factor (G-CSF), and TNF-α and hyperexpression in the plasma concentrations of IL-2, IL-7, IL-17, IL-10, MCP-1, MIP-1A, and TNF-α with consequent evolution to respiratory insufficiency. These findings demonstrate a probable and important association among severity of COVID-19 and level of the proinflammatory cytokines and subsets of immune cells, beyond to presents immune profile differences in comparison with SARS-CoV1.

During others coronavirus infections were observed besides elevated serum cytokine and chemokine levels, higher number of neutrophils and
monocytes in the patient lung and peripheral blood, suggesting an important role in lung pathology to these cells.\textsuperscript{54–46}

SARS-CoV-2 infections have been demonstrated similar behavior with higher production of cytokines as IFN-1 and/or IFN-α/β in the innate immune response, mainly, in the early stages of infection\textsuperscript{57,58} and chemokines that increase rapidly inflammatory infiltrate blood cells into lung tissue and, consequently, causing injury and, probably, playing an important role in pathogenesis to this virus.\textsuperscript{59,60}

Use of corticosteroids could be considered if hyperinflammation is present,\textsuperscript{31} but immunosuppression in infected patients might be inadvisable. Inhibit antiviral immunity can delay virus clearance and maintenance illness.\textsuperscript{19} Immunosuppression by corticosteroids impairs production of IFN-1 that act, directly, to response of respiratory virus like SARS-CoV-2.\textsuperscript{61,62}

Immunological action of corticosteroids occurs by inhibition selective to JAK-STAT signaling way, being a major component of the IFN-1 pathway.\textsuperscript{61} Inhibit inflammatory mediators, however, can contribute to secondary bacterial infection and complicate the disease course.\textsuperscript{61} Corticoids use in COVID-19 is still controversial because it may impair anti-microbial immune response.\textsuperscript{63}

\section*{IV. CHANGE FOR PHENOTYPES OF MONOCYTES}

Dysregulation of cellular functions in monocytes and macrophages, generally, are found in viral infections and to natural factors as senescence.\textsuperscript{54–66} Higher proportions of non-classical monocytes and reduced circulating proportions of classical monocytes are primary hallmark in the response exchange of these cells.\textsuperscript{67–73} In healthy individuals, reference values of classical monocytes are about 80–95% of blood circulating monocytes and non-classical monocytes about 2–11% of blood circulating monocytes.\textsuperscript{69} Although monocytes that present classical profile are highly phagocytic, non-classical cells are associated with endothelium regulation against injuries.\textsuperscript{68}

Aging-associated phenotype is consistent with the monocyte phenotypes observed in severe COVID-19 it is highly plausible that monocyte dysfunction could play a key role in increasing SARS-CoV-2 pathogenesis in older adults.\textsuperscript{72} Impairments in phagocytosis\textsuperscript{70} and reduced HLA-DR expression,\textsuperscript{69} together, suggest that aging induces an increase general shift pro-inflammatory, dysfunctional monocytes with higher expression of CD16+ molecules which configure intermediate or non-classical profile.

Angiotensin-converting enzyme 2 (ACE2) cellular receptor was identified as the primary interaction site for SARS-CoV-2\textsuperscript{74,75} and monocytes and macrophages express ACE2,\textsuperscript{76,77} making them potentially susceptible to infection.\textsuperscript{77} Infected patients to SARS-CoV-2 displayed monocytes with reduced levels of ACE2 receptor compared with noninfected individuals\textsuperscript{78} and evidences suggest that lower expressions of ACE2 receptor is a probable cause of lung inflammatory cell infiltration and that conditions in which ACE2 is already reduced may exacerbate the severity of COVID-19, but, on the other hand, the downregulation of ACE2 expression may still need to configure a protective factor against COVID-19.\textsuperscript{79}

Monocyte response alterations also display increased basal cytokine production, and this evidence was proved in comparison these cells among older and younger adults.\textsuperscript{70} Over time monocytes presents reduced mitochondrial function,\textsuperscript{80,81} which may enhance their reliance on proinflammatory glycolysis for ATP production,\textsuperscript{81} thereby contributing to a mild proinflammatory activation phenotype.

Monocytes and macrophages can represent an important way of viral dissemination in the host outside of the pulmonary system.\textsuperscript{80} Studies identified macrophages in lymph nodes and spleens to be positive for SARS-CoV-2 nucleocapsid protein antigens being associated with severe pathology of those organs.\textsuperscript{52}

\section*{V. SEVERE COVID-19 CASES ASSOCIATED WITH IMMUNOSENESCENCE AND SEDENTARISM}

SARS-CoV-2 infections causes a disproportionate number of severe cases and deaths in older adults associating senescence as the principal
risk factor for COVID-19 complications. Dysregulations of immune function and inflammatory process in these patients have been extensively reviewed and speculated that immunosenescence is a key determinant of outcomes in SARS-CoV-2 infections.

Factors natural as aging may to cause deterioration of the immune system being characterized by a series of biological events imposing metabolic alterations caused by unhealthy lifestyles and prolonged physiological stress. Naturally, aging can be associated with atrophy of the thymic structure and, consequently, activity and reduction of primary lymphopoiesis, directing to a decline in naïve T-cells, accumulation of memory T-cells, and a decrease in antibody production.

The immunosenescence stage induce changes in cell phenotype such as expression and function of receptors for leukocytes, which contributes, consequently, to loss of immune function, mainly, of chemotaxis and intracellular killing. These alterations, obviously, decrease the response against pathogens, which leads to several age-related diseases including cardiovascular alterations, diabetes and Alzheimer’s disease to older individuals.

Decline in hematopoietic stem cells (HSCs) and progenitor cell function which results in increased production of myeloid lineage cells and a decrease in lymphoid potential and still a reduction in humoral and cellular immunity, increase in the inflammatory and oxidation background and production and release of auto-antibodies leading to the insurgence of autoimmune disorders promoting changes that favor the evolution of the virus replicative cycle. A high association among aging and referred decline in HSCs beyond progenitor cell function besides changes in the production of myeloid cells and lymphoid potential it has been demonstrated.

Moreover, senescence still changes the inflammatory state by increase secretion of pro-inflammatory cytokines and this event is known as the senescence-associated secretory phenotype and contributing to the aging process. Increased production of auto-antibodies are also observed, leading to a higher number of autoimmune events and manifestations among the elderly.

Reduction of physical activity and sedentarism is one of big problem of aging and can promote alterations on glucose homeostasis and causing deleterious effects in patients as bone fractures, multiple sclerosis, hemiplegia and others. It is established that sedentarism is related with increased mortality and morbidity associated with metabolic syndromes and cardiovascular diseases.

Studies have shown that about 50% of the immune protective factors associated physical activity are accounted for by a reduction of traditional cardiovascular risk factors, such as high blood pressure and blood lipids and, consequently, to decrease inflammation of visceral fat tissue and insulin resistance, because induce positive effects on the peripheral circulation, increasing vasodilation and new angiogenesis.

In the SARS-CoV-2 pandemic, people worldwide are being confined to lower social activity and stay-at-home restrictions, reducing considerably and very quickly form, the level of daily physical activity. The importance of physical active to health body and better maintenance of the immune system is consensus and the present situation will exacerbate health problems coming from physical inactivity.

VI. MALNUTRITION AND BAD PROGNOSIS FOR SARS-COV-2

Elderly patients with COVID-19 in association with malnutrition stage causes a consume unbalance to protein that made up muscles due the increase inflammatory response by SARS-CoV-2 and high indicators production such as C-reactive protein, ferritin, tumor necrosis factor alpha and IL family factors.

The synthesis of these acute-phase proteins requires the consumption of albumin and muscle protein however, the albumin levels present significantly lower in COVID-19 patients, been this indicator is one of bigger commonly used for evaluating malnutrition.

Gastrointestinal symptoms caused by SARS-CoV-2 have exacerbated malnutrition in symptomatic patients and studies report that the virus can attack the mucosal epithelium gastrointestinal
which further damage the nutritional status of these patients.\textsuperscript{11,112}

Recent evidence examining adults infected with COVID-19 has indicated a significant impact of malnutrition\textsuperscript{114} which may influence in decrease immune function.\textsuperscript{110,113} In general, COVID-19 can evolve to symptoms as fever, cough, shortness of breath, muscle ache, confusion, headache, sore throat, chest pain, pneumonia, diarrhea, nausea, vomiting, and loss of taste and smell.\textsuperscript{115,116}

Individuals who have multiple comorbidities, older adults or who are malnourished are at increased risk of being admitted to the intensive care unit and of mortality from COVID-19 infections.\textsuperscript{114} Thereby is evident that an adequate nutrition plays an important role in the prevention and treatment of various diseases, including viral infections like SARS-CoV-2.\textsuperscript{116}

VII. CONCLUSIONS

The immune reactions during SARS-CoV-2 infection induces hyperexpression in the levels of pro-inflammatory cytokines, the increase in the inflammatory infiltrate and change for monocytes and macrophages profile, as well as important variations to the number of lymphocytes following to a severe disease profile, mainly with a destruction of lung tissue. The large number of severe cases and deaths associated with older adults is related to the senescence of the immune system in these patients. Therefore, a complete understanding of the main immunological disorders involved in SARS-CoV-2 infection paves the way to identify possible biomarkers in the early prognosis of possible serious cases of COVID-19, increasing the therapeutic success in these cases.

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